=> fil reg

FILE 'REGISTRY' ENTERED AT 11:17:06 ON 28 OCT 2000
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

STRUCTURE FILE UPDATES: 27 OCT 2000 HIGHEST RN 300341-74-6
DICTIONARY FILE UPDATES: 27 OCT 2000 HIGHEST RN 300341-74-6

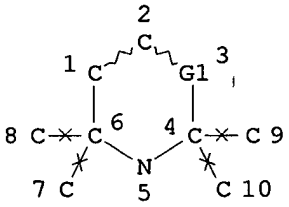
TSCA INFORMATION NOW CURRENT THROUGH July 8, 2000

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT for details.

=> d sta que l43

L36 STR

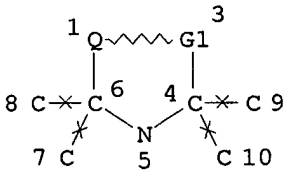


Structures are open

REP G1=(0-20) C
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 10

STEREO ATTRIBUTES: NONE
L40 STR



REP G1=(1-20) C
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 9

STEREO ATTRIBUTES: NONE
L43 33021 SEA FILE=REGISTRY SSS FUL L36 OR L40

100.0% PROCESSED 100633 ITERATIONS 33021 ANSWERS
SEARCH TIME: 00.00.15

Point of Contact:
Jan Delaval
Librarian-Physical Sciences
CM1 1E01 Tel: 308-4498

=> d his

```
     (FILE 'HOME' ENTERED AT 10:03:58 ON 28 OCT 2000)
                SET COST OFF

     FILE 'REGISTRY' ENTERED AT 10:04:08 ON 28 OCT 2000
                E TEMPOL/CN
L1            1 S E3
L2           29 S 2226-96-2/CRN

     FILE 'HCAPLUS' ENTERED AT 10:04:37 ON 28 OCT 2000
L3         1666 S L1 OR L2
L4         2326 S TEMPO OR HTEMPO OR TYTEMPO OR TEMPOL OR TEMPO OH OR TANOL OR
L5         3472 S L3,L4
                E MITCHEL J/AU
L6            2 S E3,E4
                E MITCHELL J/AU
L7          375 S E3,E5-E8
                E MITCHELL JAMES/AU
L8          173 S E3,E6-E8
                E RUSSO A/AU
L9          335 S E3-E16,E42
                E KRISHNA M/AU
L10         193 S E3-E26
L11          55 S E49-E51
                E DELUCA A/AU
L12          19 S E3,E4,E11,E13,E14
                E DE LUCA A/AU
L13          52 S E3,E4,E11
                E LUCA A/AU
L14        1063 S L6-L13
L15          32 S L5 AND L14
L16          49 S NITROXIDE AND L14
L17          52 S L15,L16
L18        1011 S L14 NOT L17

     FILE 'REGISTRY' ENTERED AT 10:08:56 ON 28 OCT 2000

     FILE 'HCAPLUS' ENTERED AT 10:08:57 ON 28 OCT 2000
                SET SMARTSELECT ON
L19          SEL L17 1- RN :     216 TERMS
                SET SMARTSELECT OFF

     FILE 'REGISTRY' ENTERED AT 10:09:01 ON 28 OCT 2000
L20          216 S L19

     FILE 'HCAPLUS' ENTERED AT 10:09:15 ON 28 OCT 2000
                SET SMARTSELECT ON
L21          SEL L18 1- RN :    1717 TERMS
                SET SMARTSELECT OFF

     FILE 'REGISTRY' ENTERED AT 10:09:58 ON 28 OCT 2000
L22         1715 S L21
L23            1 S L20 AND L1,L2
L24            0 S L22 AND L1,L2
L25         1906 S L20,L22
L26           62 S L25 AND (NC5 OR NC6 OR NC7 OR NC8 OR NC9 OR NC10 OR NC11 OR N
L27           21 S L26 AND 46.156.30/RID
L28           41 S L26 NOT L27
L29           11 S L28 AND (C16H15F3N2O4 OR C22H28N2O OR C9H20N2O3S OR C20H25NO2
L30           30 S L28 NOT L29
L31           59 S L1,L2,L30,L23
                SAV L31 KWON424/A
L32             STR
L33             STR L32
```

```
L34          13 S L32 OR L32
L35          50 S L33
L36             STR L33
L37          50 S L36
L38             STR L36
L39          12 S L38
L40             STR L38
L41          50 S L40
L42          50 S L36 OR L40
L43       33021 S L36 OR L40 FUL
                SAV TEMP L43 KWON424A/A
L44         150 S L25 AND L43
L45          30 S L31 AND L44
L46         120 S L44 NOT L45
L47         179 S L31,L44-L46
L48       33021 S L43,L47

     FILE 'HCAPLUS' ENTERED AT 10:50:59 ON 28 OCT 2000
L49       16397 S L48
L50       21356 S L5 OR L49 OR NITROXIDE
L51          52 S L50 AND L14
L52         543 S L50 AND (ONCOLOG? OR ?NEOPLAS? OR ?CANCER? OR ?CARCIN? OR ?ME
L53          28 S L50 AND (SUPPRES? (L) GENE?)
L54          25 S L50 AND (REGULAT? (L) GENE?)
L55           3 S L50 AND P53
L56           9 S L52 AND L53,L54
L57          60 S L51,L56
L58       13800 S L50 AND (PD<=19921209 OR PRD<=19921209 OR PRD.B<=19921209 OR
L59          15 S L58 AND L51
L60          13 S L58 AND L53,L54
L61          15 S L58 AND L57
L62          28 S L59-L61
L63         211 S L50 AND (?MUTAGEN? OR ?MUTANT? OR ?MUTAT?)
L64          77 S L58 AND L63
L65          98 S L62,L64
L66          13 S L65 AND (1 OR 63 OR 15)/SC
L67           7 S L52 AND L66
L68          20 S L52 AND L65
L69          26 S L66-L68
L70           0 S L55 AND L58
L71          29 S L55,L69
L72       18388 S L50 AND (PD<=19970527 OR PRD<=19970527 OR PRD.B<=19970527 OR
L73           5 S L72 AND L55,L56
L74          41 S L72 AND L57
L75         572 S L72 AND (L52 OR ?MUTAGEN? OR ?MUTANT? OR ?MUTAT?)
L76           2 S L75 AND P53
L77          20 S L75 AND L51
L78          10 S L75 AND (SUPPRES? OR REGULAT?)(L)GENE?
L79           5 S L75 AND (SUPPRES? OR REGULAT?)(L)DNA
L80           0 S L75 AND (SUPPRES? OR REGULAT?)(L)CDNA
L81           0 S L75 AND (SUPPRES? OR REGULAT?)(L)RNA
L82           1 S L75 AND (SUPPRES? OR REGULAT?)(L)MRNA
L83          42 S L71,L73,L74,L76-L82 AND L49
L84          28 S L71,L73,L74,L76-L82 AND L3
L85          44 S L71,L73,L74,L76-L82 AND NITROXIDE
L86          57 S L83-L85
L87          34 S L86 AND (1 OR 15 OR 63 OR 8)/SC
L88           9 S L86 AND (1 OR 15 OR 63 OR 8)/SX
L89          38 S L87,L88
                E KRISHNA C/AU
L90          60 S E3-E5,E14
L91           7 S L90 AND L89
L92          38 S L89,L91
                E CHERUKURI/AU
L93           4 S E12-E14
L94           1 S L93 AND L92
```

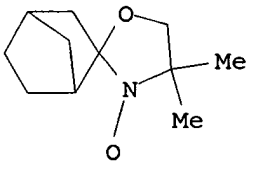
```
L95          15 S L90,L93 AND L72
L96          10 S L95 AND L86
L97           2 S L96 NOT L92
L98          57 S L86,L96
L99          38 S L98 AND (1 OR 15 OR 63 OR 8)/SC,SX
L100         19 S L98 NOT L99
L101         57 S L98-L100
L102          4 S L101 AND P/DT
L103         57 S L101,L102
                SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 11:16:32 ON 28 OCT 2000
L104         68 S E1-E68

     FILE 'REGISTRY' ENTERED AT 11:17:06 ON 28 OCT 2000

=> d ide can tot l104


L104 ANSWER 1 OF 68  REGISTRY  COPYRIGHT 2000 ACS
RN   186664-92-6  REGISTRY
CN   Spiro[bicyclo[2.2.1]heptane-2,2'-oxazolidin]-3'-yloxy, 4',4'-dimethyl-
     (9CI)  (CA INDEX NAME)
MF   C11 H18 N O2
SR   CA
LC   STN Files:   CA, CAPLUS, TOXLIT
```

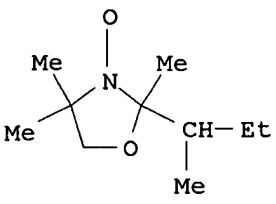


Hit cmpds for rep 1-57, L103

```
                1 REFERENCES IN FILE CA (1967 TO DATE)
                1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE   1:  126:139898

L104 ANSWER 2 OF 68  REGISTRY  COPYRIGHT 2000 ACS
RN   186664-91-5  REGISTRY
CN   3-Oxazolidinyloxy, 2,4,4-trimethyl-2-(1-methylpropyl)- (9CI)  (CA INDEX
     NAME)
MF   C10 H20 N O2
SR   CA
LC   STN Files:   CA, CAPLUS, TOXLIT
```

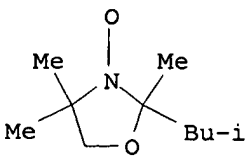



```
                1 REFERENCES IN FILE CA (1967 TO DATE)
                1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE   1:  126:139898

L104 ANSWER 3 OF 68  REGISTRY  COPYRIGHT 2000 ACS
RN   186664-90-4  REGISTRY
```

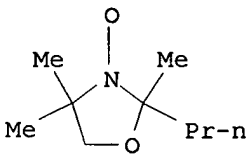
CN 3-Oxazolidinyloxy, 2,4,4-trimethyl-2-(2-methylpropyl)- (9CI) (CA INDEX NAME)
MF C10 H20 N O2
SR CA
LC STN Files: CA, CAPLUS, TOXLIT



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:139898

L104 ANSWER 4 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **186664-89-1** REGISTRY
CN 3-Oxazolidinyloxy, 2,4,4-trimethyl-2-propyl- (9CI) (CA INDEX NAME)
MF C9 H18 N O2
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

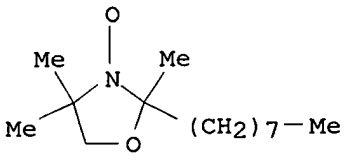


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:211183

REFERENCE 2: 126:139898

L104 ANSWER 5 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **174153-11-8** REGISTRY
CN 3-Oxazolidinyloxy, 2,4,4-trimethyl-2-octyl- (9CI) (CA INDEX NAME)
MF C14 H28 N O2
SR CA
LC STN Files: CA, CAPLUS, CASREACT, TOXLIT

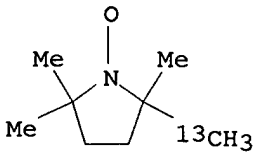


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:139898

REFERENCE 2: 124:202078

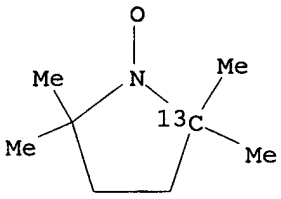
L104 ANSWER 6 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **157686-99-2** REGISTRY
CN 1-Pyrrolidinyloxy, 2,2,5-trimethyl-5-(methyl-13C)- (9CI) (CA INDEX NAME)
MF C8 H16 N O
SR CA
LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 121:179003

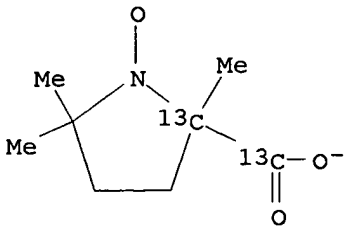
L104 ANSWER 7 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **157686-98-1** REGISTRY
CN 1-Pyrrolidinyl-2-13C-oxy, 2,2,5,5-tetramethyl- (9CI) (CA INDEX NAME)
MF C8 H16 N O
SR CA
LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 121:179003

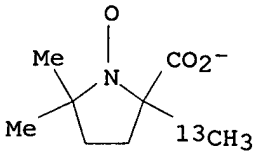
L104 ANSWER 8 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **157686-95-8** REGISTRY
CN 1-Pyrrolidinyl-2-13C-oxy, 2-(carboxy-13C)-2,5,5-trimethyl-, ion(1-) (9CI)
(CA INDEX NAME)
MF C8 H13 N O3
SR CA
LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 121:179003

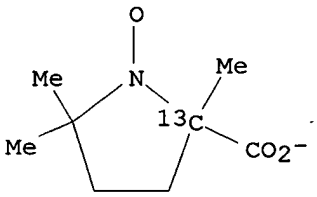
L104 ANSWER 9 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **157686-94-7** REGISTRY
CN 1-Pyrrolidinyloxy, 2-carboxy-5,5-dimethyl-2-(methyl-13C)-, ion(1-) (9CI) (CA INDEX NAME)
MF C8 H13 N O3
SR CA
LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 121:179003

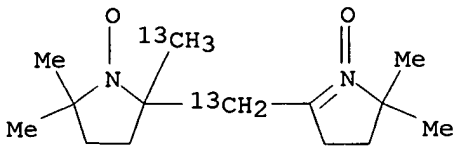
L104 ANSWER 10 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **157686-93-6** REGISTRY
CN 1-Pyrrolidinyl-2-13C-oxy, 2-carboxy-2,5,5-trimethyl-, ion(1-) (9CI) (CA INDEX NAME)
MF C8 H13 N O3
SR CA
LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 121:179003

L104 ANSWER 11 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **157686-92-5** REGISTRY
CN 1-Pyrrolidinyloxy, 2-[(3,4-dihydro-2,2-dimethyl-1-oxido-2H-pyrrol-5-yl)methyl-13C]-5,5-dimethyl-2-(methyl-13C)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1-Pyrrolidinyloxy, 2-[(3,4-dihydro-2,2-dimethyl-2H-pyrrol-5-yl)methyl-13C]-5,5-dimethyl-2-(methyl-13C)-, N-oxide
MF C14 H25 N2 O2
SR CA
LC STN Files: CA, CAPLUS

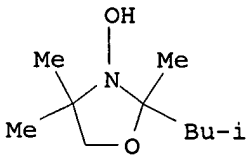


1 REFERENCES IN FILE CA (1967 TO DATE)

1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 121:179003

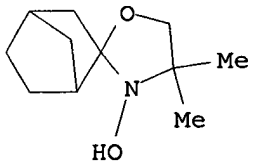
L104 ANSWER 12 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **136567-25-4** REGISTRY
CN Oxazolidine, 3-hydroxy-2,4,4-trimethyl-2-(2-methylpropyl)- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C10 H21 N O2
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 115:177284

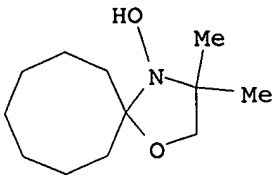
L104 ANSWER 13 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **135301-19-8** REGISTRY
CN Spiro[bicyclo[2.2.1]heptane-2,2'-oxazolidine], 3'-hydroxy-4',4'-dimethyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C11 H19 N O2
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 115:177284

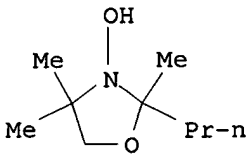
L104 ANSWER 14 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **135301-18-7** REGISTRY
CN 1-Oxa-4-azaspiro[4.7]dodecane, 4-hydroxy-3,3-dimethyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C12 H23 N O2
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 115:177284

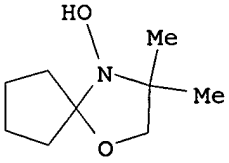
L104 ANSWER 15 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **135301-17-6** REGISTRY
CN Oxazolidine, 3-hydroxy-2,4,4-trimethyl-2-propyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C9 H19 N O2
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 115:177284

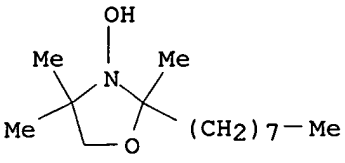
L104 ANSWER 16 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **135273-99-3** REGISTRY
CN 1-Oxa-4-azaspiro[4.4]nonane, 4-hydroxy-3,3-dimethyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C9 H17 N O2
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 115:177284

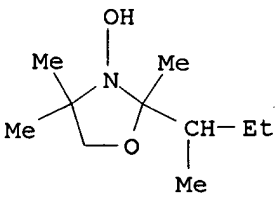
L104 ANSWER 17 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **135273-98-2** REGISTRY
CN Oxazolidine, 3-hydroxy-2,4,4-trimethyl-2-octyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C14 H29 N O2
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 115:177284

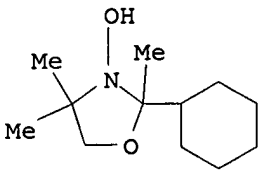
L104 ANSWER 18 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **135273-97-1** REGISTRY
CN Oxazolidine, 3-hydroxy-2,4,4-trimethyl-2-(1-methylpropyl)- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C10 H21 N O2
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 115:177284

L104 ANSWER 19 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **135273-96-0** REGISTRY
CN Oxazolidine, 2-cyclohexyl-3-hydroxy-2,4,4-trimethyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C12 H23 N O2
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

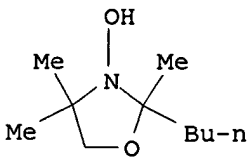


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 115:177284

L104 ANSWER 20 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **135273-95-9** REGISTRY
CN Oxazolidine, 2-butyl-3-hydroxy-2,4,4-trimethyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD

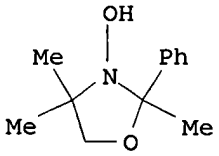
MF C10 H21 N O2
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 115:177284

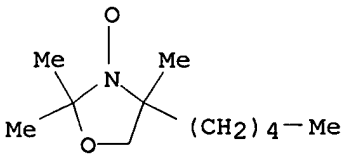
L104 ANSWER 21 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **135273-94-8** REGISTRY
CN Oxazolidine, 3-hydroxy-2,4,4-trimethyl-2-phenyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C12 H17 N O2
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 115:177284

L104 ANSWER 22 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **134998-34-8** REGISTRY
CN 3-Oxazolidinyloxy, 2,2,4-trimethyl-4-pentyl- (9CI) (CA INDEX NAME)
MF C11 H22 N O2
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

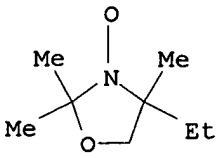


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 115:64685

L104 ANSWER 23 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **134998-33-7** REGISTRY
CN 3-Oxazolidinyloxy, 4-ethyl-2,2,4-trimethyl- (9CI) (CA INDEX NAME)
MF C8 H16 N O2
SR CA

LC STN Files: CA, CAPLUS, TOXLIT

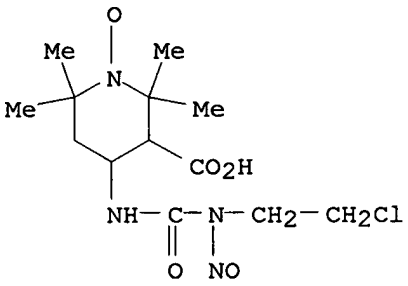


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:132804

REFERENCE 2: 115:64685

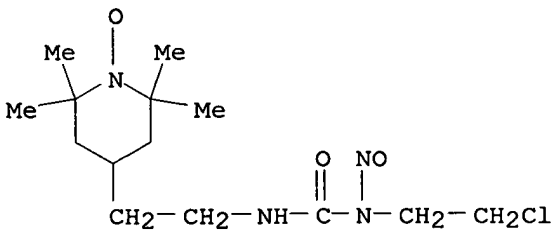
L104 ANSWER 24 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **132414-36-9** REGISTRY
CN 1-Piperidinyloxy, 3-carboxy-4-[[[(2-chloroethyl)nitrosoamino]carbonyl]amino]-2,2,6,6-tetramethyl- (9CI) (CA INDEX NAME)
MF C13 H22 Cl N4 O5
SR CA
LC STN Files: CA, CAPLUS, TOXLIT



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 114:157185

L104 ANSWER 25 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **132414-35-8** REGISTRY
CN 1-Piperidinyloxy, 4-[2-[[[(2-chloroethyl)nitrosoamino]carbonyl]amino]ethyl]-2,2,6,6-tetramethyl- (9CI) (CA INDEX NAME)
MF C14 H26 Cl N4 O3
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

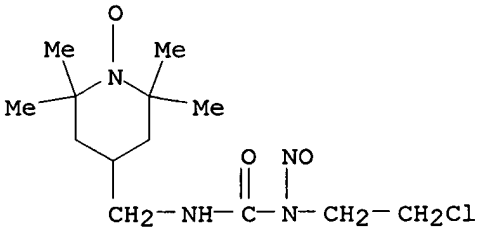


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:86794

REFERENCE 2: 114:157185

L104 ANSWER 26 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **132414-34-7** REGISTRY
CN 1-Piperidinyloxy, 4-[[[[(2-chloroethyl)nitrosoamino]carbonyl]amino]methyl]-2,2,6,6-tetramethyl- (9CI) (CA INDEX NAME)
MF C13 H24 Cl N4 O3
SR CA
LC STN Files: CA, CAPLUS, TOXLIT



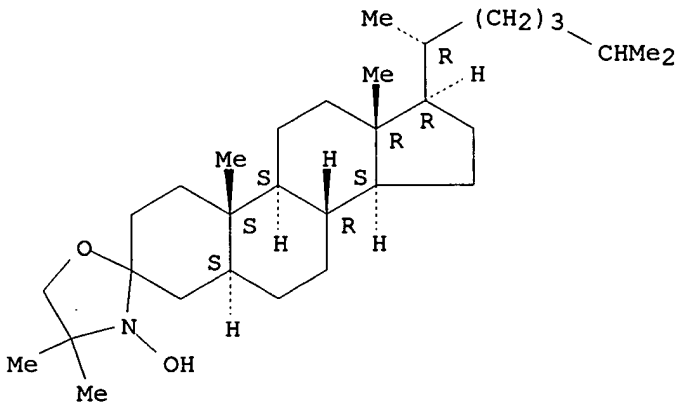
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:86794

REFERENCE 2: 114:157185

L104 ANSWER 27 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **128821-74-9** REGISTRY
CN Spiro[cholestane-3,2'-oxazolidine], 3'-hydroxy-4',4'-dimethyl-, (5.alpha.)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Spiro[3H-cyclopenta[a]phenanthrene-3,2'-oxazolidine], spiro[cholestane-3,2'-oxazolidine] deriv.
OTHER NAMES:
CN IK 3
CN IK 3 (steroid)
FS STEREOSEARCH
MF C31 H55 N O2
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

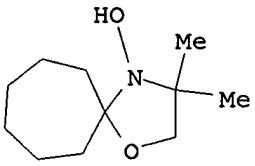
REFERENCE 1: 127:304157

REFERENCE 2: 115:177284

REFERENCE 3: 115:7737

REFERENCE 4: 113:96665

L104 ANSWER 28 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **128757-79-9** REGISTRY
CN 1-Oxa-4-azaspiro[4.6]undecane, 4-hydroxy-3,3-dimethyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C11 H21 N O2
SR CA
LC STN Files: CA, CAPLUS, CASREACT, TOXLIT, USPATFULL



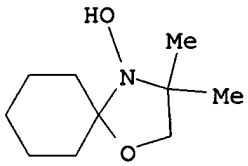
3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 115:177284

REFERENCE 2: 115:7737

REFERENCE 3: 113:96665

L104 ANSWER 29 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **128757-78-8** REGISTRY
CN 1-Oxa-4-azaspiro[4.5]decane, 4-hydroxy-3,3-dimethyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C10 H19 N O2
SR CA
LC STN Files: CA, CAPLUS, CASREACT, TOXLIT, USPATFULL



6 REFERENCES IN FILE CA (1967 TO DATE)
6 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:208292

REFERENCE 2: 130:169756

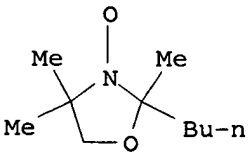
REFERENCE 3: 126:238014

REFERENCE 4: 115:177284

REFERENCE 5: 115:7737

REFERENCE 6: 113:96665

L104 ANSWER 30 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **125569-48-4** REGISTRY
CN 3-Oxazolidinyloxy, 2-butyl-2,4,4-trimethyl- (9CI) (CA INDEX NAME)
MF C10 H20 N O2
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

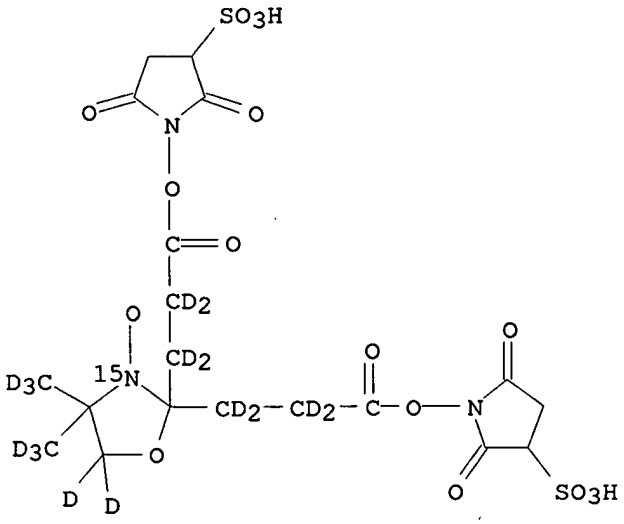


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:139898

REFERENCE 2: 112:135122

L104 ANSWER 31 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **115420-14-9** REGISTRY
CN 3-Oxazolidinyl-5,5-d2-3-15N-oxy, 2,2-bis[3-[(2,5-dioxo-3-sulfo-1-pyrrolidinyl)oxy]-3-oxopropyl-1,1,2,2-d4]-4,4-di(methyl-d3)- (9CI) (CA INDEX NAME)
MF C19 H8 D16 N3 O16 S2
SR CA
LC STN Files: CA, CAPLUS, TOXLIT



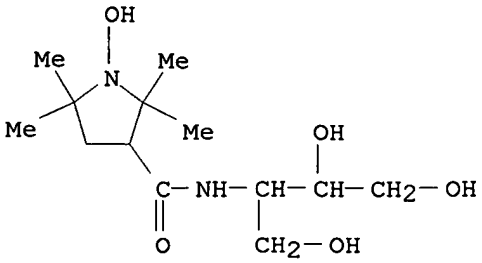
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 119:86354

REFERENCE 2: 109:107224

L104 ANSWER 32 OF 68 REGISTRY COPYRIGHT 2000 ACS

RN **113788-70-8** REGISTRY
CN 3-Pyrrolidinecarboxamide, N-[2,3-dihydroxy-1-(hydroxymethyl)propyl]-1-hydroxy-2,2,5,5-tetramethyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C13 H26 N2 O5
SR CA
LC STN Files: CA, CAPLUS, PHAR, TOXLIT

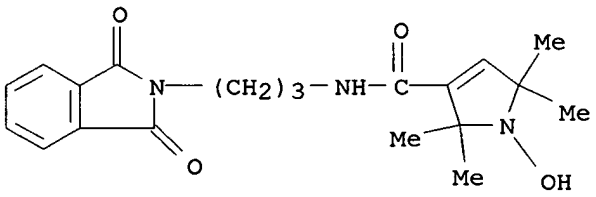


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 109:163475

REFERENCE 2: 108:164118

L104 ANSWER 33 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **102132-51-4** REGISTRY
CN 1H-Pyrrole-3-carboxamide, N-[3-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)propyl]-2,5-dihydro-1-hydroxy-2,2,5,5-tetramethyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C20 H25 N3 O4
CI COM
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXLIT
(*File contains numerically searchable property data)



5 REFERENCES IN FILE CA (1967 TO DATE)
5 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:317794

REFERENCE 2: 129:184261

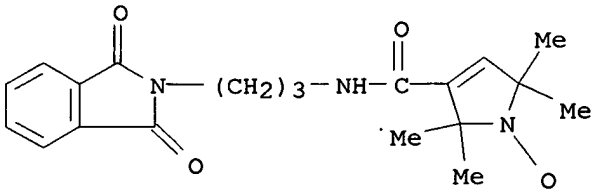
REFERENCE 3: 126:195017

REFERENCE 4: 106:18297

REFERENCE 5: 105:24144

L104 ANSWER 34 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **102132-45-6** REGISTRY
CN 1H-Pyrrol-1-yloxy, 3-[[[3-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)propyl]amino]carbonyl]-2,5-dihydro-2,2,5,5-tetramethyl- (9CI) (CA

INDEX NAME)
MF C20 H24 N3 O4
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, RTECS*, TOXLIT
(*File contains numerically searchable property data)



5 REFERENCES IN FILE CA (1967 TO DATE)
5 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:317794

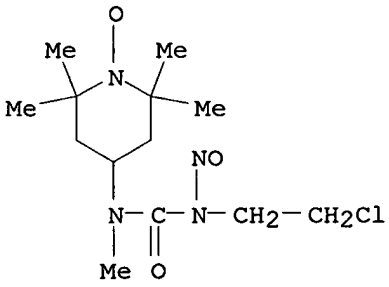
REFERENCE 2: 129:184261

REFERENCE 3: 126:195017

REFERENCE 4: 106:18297

REFERENCE 5: 105:24144

L104 ANSWER 35 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **97579-81-2** REGISTRY
CN 1-Piperidinyloxy, 4-[[[(2-chloroethyl)nitrosoamino]carbonyl]methylamino]-2,2,6,6-tetramethyl- (9CI) (CA INDEX NAME)
MF C13 H24 Cl N4 O3
SR CA
LC STN Files: CA, CAPLUS, TOXLIT



4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:86794

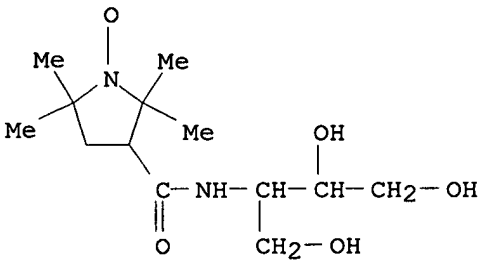
REFERENCE 2: 114:157185

REFERENCE 3: 107:228567

REFERENCE 4: 103:71165

L104 ANSWER 36 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **97546-74-2** REGISTRY
CN 1-Pyrrolidinyloxy, 3-[[[2,3-dihydroxy-1-(hydroxymethyl)propyl]amino]carbonyl]-2,2,5,5-tetramethyl- (9CI) (CA INDEX NAME)
OTHER NAMES:

CN Pyrroxamide
CN Troxolamide
MF C13 H25 N2 O5
SR CA
LC STN Files: BEILSTEIN*, BIOSIS, CA, CANCERLIT, CAPLUS, IPA, MEDLINE, TOXLINE, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO



6 REFERENCES IN FILE CA (1967 TO DATE)
6 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 121:199724

REFERENCE 2: 117:103606

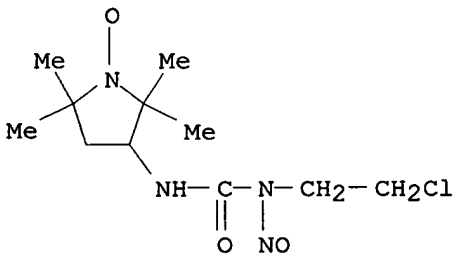
REFERENCE 3: 113:90682

REFERENCE 4: 109:163475

REFERENCE 5: 108:164118

REFERENCE 6: 103:71185

L104 ANSWER 37 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **97241-83-3** REGISTRY
CN 1-Pyrrolidinyloxy, 3-[[[(2-chloroethyl)nitrosoamino]carbonyl]amino]-2,2,5,5-tetramethyl- (9CI) (CA INDEX NAME)
MF C11 H20 Cl N4 O3
LC STN Files: CA, CAPLUS, TOXLIT



7 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
7 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:86794

REFERENCE 2: 115:183727

REFERENCE 3: 114:157185

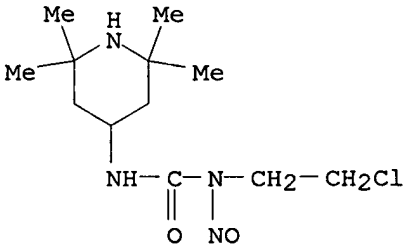
REFERENCE 4: 112:171749

REFERENCE 5: 111:187017

REFERENCE 6: 107:228567

REFERENCE 7: 103:32012

L104 ANSWER 38 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **95596-73-9** REGISTRY
CN Urea, N-(2-chloroethyl)-N-nitroso-N'-(2,2,6,6-tetramethyl-4-piperidinyl)-(9CI) (CA INDEX NAME)
OTHER NAMES:
CN R50
FS 3D CONCORD
MF C12 H23 Cl N4 O2
CI COM
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXLIT
(*File contains numerically searchable property data)



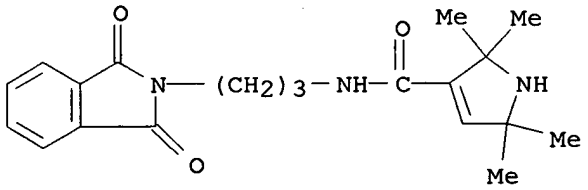
3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 106:133483

REFERENCE 2: 104:148699

REFERENCE 3: 102:142859

L104 ANSWER 39 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **93799-37-2** REGISTRY
CN 1H-Pyrrole-3-carboxamide, N-[3-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)propyl]-2,5-dihydro-2,2,5,5-tetramethyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN A 2545
FS 3D CONCORD
MF C20 H25 N3 O3
CI COM
LC STN Files: ANABSTR, BEILSTEIN*, CA, CAPLUS, DDFU, DRUGNL, DRUGU, DRUGUPDATES, IPA, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)



9 REFERENCES IN FILE CA (1967 TO DATE)
9 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:317794

REFERENCE 2: 130:204826

REFERENCE 3: 129:78

REFERENCE 4: 128:110359

REFERENCE 5: 126:195017

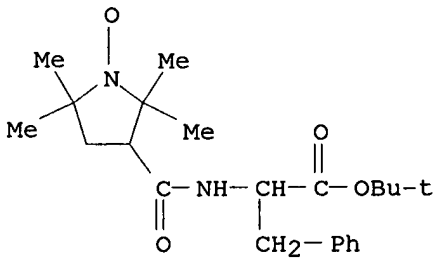
REFERENCE 6: 125:204323

REFERENCE 7: 106:18297

REFERENCE 8: 105:24144

REFERENCE 9: 102:24471

L104 ANSWER 40 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **92455-23-7** REGISTRY
CN 1-Pyrrolidinyloxy, 3-[[[2-(1,1-dimethylethoxy)-2-oxo-1-(phenylmethyl)ethyl]amino]carbonyl]-2,2,5,5-tetramethyl- (9CI) (CA INDEX NAME)
MF C22 H33 N2 O4
LC STN Files: CA, CAPLUS, MEDLINE, TOXLIT



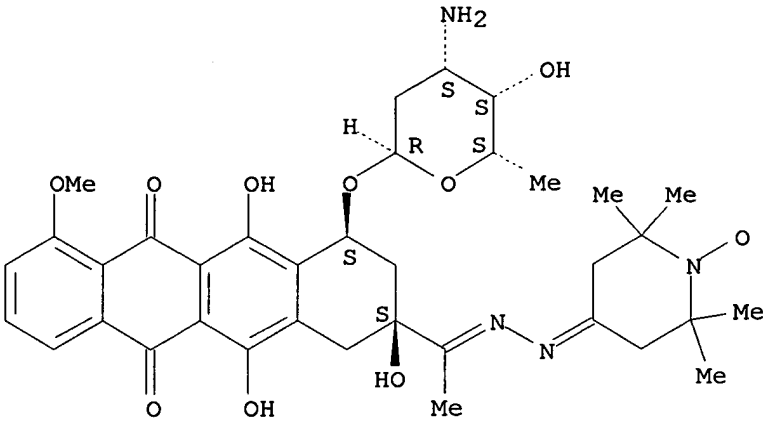
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 105:145894

REFERENCE 2: 101:163410

L104 ANSWER 41 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **84412-94-2** REGISTRY
CN 1-Piperidinyloxy, 4-[[1-[(2S,4S)-4-[(3-amino-2,3,6-trideoxy-.alpha.-L-lyxo-hexopyranosyl)oxy]-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-2-naphthacenyl]ethylidene]hydrazono]-2,2,6,6-tetramethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1-Piperidinyloxy, 4-[[1-[4-[(3-amino-2,3,6-trideoxy-.alpha.-L-lyxo-hexopyranosyl)oxy]-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-2-naphthacenyl]ethylidene]hydrazono]-2,2,6,6-tetramethyl-, (2S-cis)-
OTHER NAMES:
CN Emoxyl
CN Ruboxyl
CN Ruboxyl 1
FS STEREOSEARCH
DR 83138-78-7
MF C36 H45 N4 O10
CI COM
LC STN Files: BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, DDFU, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, RTECS*, TOXLINE, TOXLIT
(*File contains numerically searchable property data)

Absolute stereochemistry.
Double bond geometry unknown.



25 REFERENCES IN FILE CA (1967 TO DATE)
25 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:102489

REFERENCE 2: 132:69256

REFERENCE 3: 131:23332

REFERENCE 4: 130:257354

REFERENCE 5: 128:200507

REFERENCE 6: 127:195342

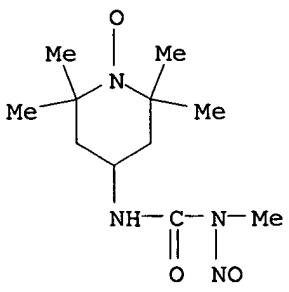
REFERENCE 7: 124:44991

REFERENCE 8: 120:289592

REFERENCE 9: 120:153180

REFERENCE 10: 119:217392

L104 ANSWER 42 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **83144-39-2** REGISTRY
CN 1-Piperidinyloxy, 2,2,6,6-tetramethyl-4-[[(methylnitrosoamino)carbonyl]amino]- (9CI) (CA INDEX NAME)
MF C11 H21 N4 O3
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXLIT
(*File contains numerically searchable property data)



7 REFERENCES IN FILE CA (1967 TO DATE)
7 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 128:18466

REFERENCE 2: 124:86794

REFERENCE 3: 115:149862

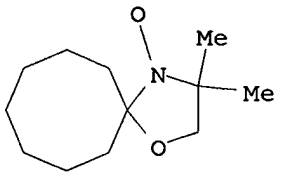
REFERENCE 4: 114:157185

REFERENCE 5: 111:187017

REFERENCE 6: 104:148699

REFERENCE 7: 97:140630

L104 ANSWER 43 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **75164-94-2** REGISTRY
CN 1-Oxa-4-azaspiro[4.7]dodec-4-yloxy, 3,3-dimethyl- (9CI) (CA INDEX NAME)
MF C12 H22 N O2
LC STN Files: CA, CAPLUS, TOXLIT

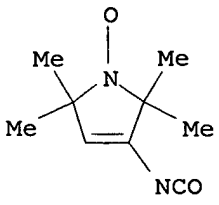


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:139898

REFERENCE 2: 93:167473

L104 ANSWER 44 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **68212-42-0** REGISTRY
CN 1H-Pyrrol-1-yloxy, 2,5-dihydro-3-isocyanato-2,2,5,5-tetramethyl- (9CI)
(CA INDEX NAME)
MF C9 H13 N2 O2
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXLIT
(*File contains numerically searchable property data)



13 REFERENCES IN FILE CA (1967 TO DATE)
13 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:254346

REFERENCE 2: 126:157335

REFERENCE 3: 125:300689

REFERENCE 4: 124:86793

REFERENCE 5: 122:314363

REFERENCE 6: 119:151772

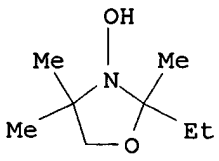
REFERENCE 7: 113:78066

REFERENCE 8: 112:235042

REFERENCE 9: 98:118237

REFERENCE 10: 96:227744

L104 ANSWER 45 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **67201-43-8** REGISTRY
CN Oxazolidine, 2-ethyl-3-hydroxy-2,4,4-trimethyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN OXANOH
FS 3D CONCORD
MF C8 H17 N O2
LC STN Files: AGRICOLA, BIOSIS, CA, CANCERLIT, CAPLUS, MEDLINE, TOXLIT, USPATFULL



12 REFERENCES IN FILE CA (1967 TO DATE)
12 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 128:70622

REFERENCE 2: 127:293151

REFERENCE 3: 127:181164

REFERENCE 4: 117:208293

REFERENCE 5: 115:177284

REFERENCE 6: 113:111000

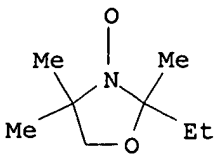
REFERENCE 7: 111:90430

REFERENCE 8: 110:3623

REFERENCE 9: 109:145617

REFERENCE 10: 97:3096

L104 ANSWER 46 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **65162-38-1** REGISTRY
CN 3-Oxazolidinyloxy, 2-ethyl-2,4,4-trimethyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-Ethyl-2,4,4-trimethyl-3-oxazolidinyloxyl
CN OXANO
MF C8 H16 N O2
LC STN Files: CA, CAPLUS, EMBASE, MEDLINE, TOXLINE, TOXLIT



20 REFERENCES IN FILE CA (1967 TO DATE)
20 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:63216

REFERENCE 2: 129:341255

REFERENCE 3: 127:293151

REFERENCE 4: 126:139898

REFERENCE 5: 126:99335

REFERENCE 6: 117:208293

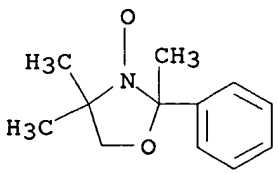
REFERENCE 7: 115:86966

REFERENCE 8: 114:243732

REFERENCE 9: 114:57081

REFERENCE 10: 113:111000

L104 ANSWER 47 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **63035-93-8** REGISTRY
CN 3-Oxazolidinyloxy, 2,4,4-trimethyl-2-phenyl- (9CI) (CA INDEX NAME)
MF C12 H16 N O2
LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXLIT
(*File contains numerically searchable property data)



4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:139898

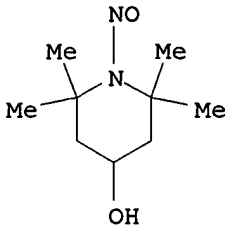
REFERENCE 2: 115:102910

REFERENCE 3: 112:135122

REFERENCE 4: 87:5287

L104 ANSWER 48 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **55556-90-6** REGISTRY
CN 4-Piperidinol, 2,2,6,6-tetramethyl-1-nitroso- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C9 H18 N2 O2
CI COM
LC STN Files: BEILSTEIN*, CA, CAPLUS, CHEMCATS, SPECINFO, TOXLINE, TOXLIT

(*File contains numerically searchable property data)



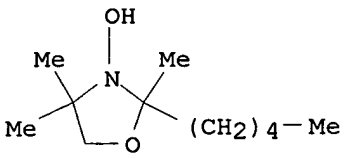
3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 90:86151

REFERENCE 2: 89:203141

REFERENCE 3: 88:59209

L104 ANSWER 49 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **55011-31-9** REGISTRY
CN Oxazolidine, 3-hydroxy-2,4,4-trimethyl-2-pentyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C11 H23 N O2
LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXLIT, USPATFULL
(*File contains numerically searchable property data)



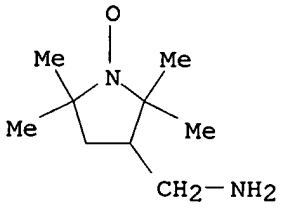
3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 115:177284

REFERENCE 2: 83:177594

REFERENCE 3: 83:164044

L104 ANSWER 50 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **54606-49-4** REGISTRY
CN 1-Pyrrolidinyloxy, 3-(aminomethyl)-2,2,5,5-tetramethyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 3-(Aminomethyl)-2,2,5,5-tetramethyl-1-pyrrolidinyloxy
MF C9 H19 N2 O
CI COM
LC STN Files: BEILSTEIN*, CA, CAPLUS, CHEMCATS, MEDLINE, MSDS-OHS, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)



38 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
38 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:27802

REFERENCE 2: 130:321570

REFERENCE 3: 130:206760

REFERENCE 4: 130:169756

REFERENCE 5: 130:68047

REFERENCE 6: 130:63216

REFERENCE 7: 130:26383

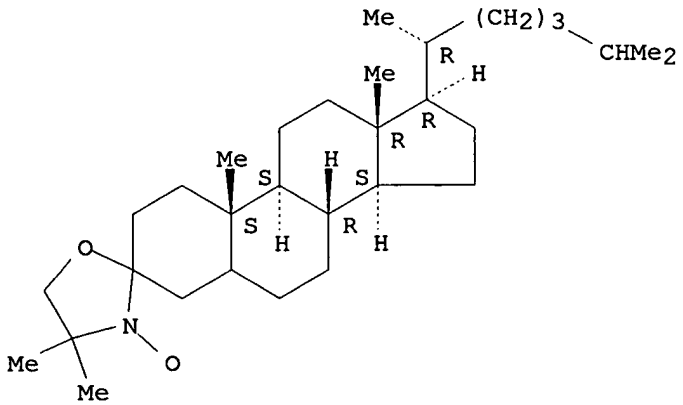
REFERENCE 8: 129:254346

REFERENCE 9: 129:230403

REFERENCE 10: 129:136490

L104 ANSWER 51 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **35328-08-6** REGISTRY
CN Spiro[cholestane-3,2'-oxazolidin]-3'-yloxy, 4',4'-dimethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Spiro[3H-cyclopenta[a]phenanthrene-3,2'-oxazolidine], spiro[cholestane-3,2'-oxazolidin]-3'-yloxy deriv.
FS STEREOSEARCH
MF C31 H54 N O2
LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXLIT
(*File contains numerically searchable property data)

Absolute stereochemistry.



10 REFERENCES IN FILE CA (1967 TO DATE)
10 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:139898

REFERENCE 2: 112:7788

REFERENCE 3: 108:183090

REFERENCE 4: 99:135863

REFERENCE 5: 96:176570

REFERENCE 6: 94:93105

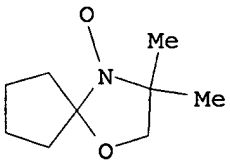
REFERENCE 7: 92:71879

REFERENCE 8: 90:199199

REFERENCE 9: 78:26110

REFERENCE 10: 76:59502

L104 ANSWER 52 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **35328-06-4** REGISTRY
CN 1-Oxa-4-azaspiro[4.4]non-4-yloxy, 3,3-dimethyl- (9CI) (CA INDEX NAME)
MF C9 H16 N O2
LC STN Files: CA, CAPLUS, TOXLIT

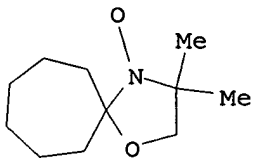


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:139898

REFERENCE 2: 76:59502

L104 ANSWER 53 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **35328-03-1** REGISTRY
CN 1-Oxa-4-azaspiro[4.6]undec-4-yloxy, 3,3-dimethyl- (9CI) (CA INDEX NAME)
MF C11 H20 N O2
LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXLIT
(*File contains numerically searchable property data)



4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

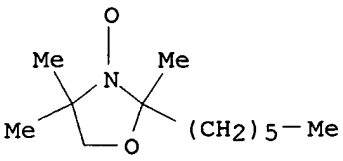
REFERENCE 1: 126:139898

REFERENCE 2: 93:167473

REFERENCE 3: 81:90679

REFERENCE 4: 76:59502

L104 ANSWER 54 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **35203-77-1** REGISTRY
CN 3-Oxazolidinyloxy, 2-hexyl-2,4,4-trimethyl- (9CI) (CA INDEX NAME)
MF C12 H24 N O2
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXLIT
(*File contains numerically searchable property data)



5 REFERENCES IN FILE CA (1967 TO DATE)
5 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:139898

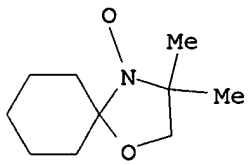
REFERENCE 2: 124:202078

REFERENCE 3: 94:55090

REFERENCE 4: 76:59502

REFERENCE 5: 76:43676

L104 ANSWER 55 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **16302-61-7** REGISTRY
CN 1-Oxa-4-azaspiro[4.5]dec-4-yloxy, 3,3-dimethyl- (8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN Doxylcyclohexane
CN Spiro[cyclohexane-1,2'-(4',4'-dimethyl-3-oxazolidinyloxy)]
MF C10 H18 N O2
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, CSCHEM, TOXLIT, USPATFULL
(*File contains numerically searchable property data)



43 REFERENCES IN FILE CA (1967 TO DATE)
43 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45141

REFERENCE 2: 130:169756

REFERENCE 3: 129:16080

REFERENCE 4: 127:307701

REFERENCE 5: 126:238014

REFERENCE 6: 126:139898

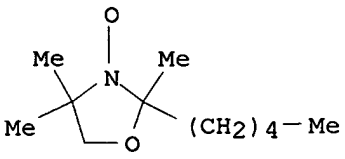
REFERENCE 7: 126:99335

REFERENCE 8: 124:344822

REFERENCE 9: 124:253122

REFERENCE 10: 123:339838

L104 ANSWER 56 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **16263-51-7** REGISTRY
CN 3-Oxazolidinyloxy, 2,4,4-trimethyl-2-pentyl- (8CI, 9CI) (CA INDEX NAME)
MF C11 H22 N O2
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXLIT
(*File contains numerically searchable property data)



8 REFERENCES IN FILE CA (1967 TO DATE)
8 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:139898

REFERENCE 2: 124:202078

REFERENCE 3: 115:102910

REFERENCE 4: 112:135122

REFERENCE 5: 83:177594

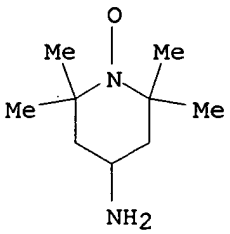
REFERENCE 6: 83:164044

REFERENCE 7: 81:90679

REFERENCE 8: 67:116837

L104 ANSWER 57 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **14691-88-4** REGISTRY
CN 1-Piperidinyloxy, 4-amino-2,2,6,6-tetramethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Piperidinooxy, 4-amino-2,2,6,6-tetramethyl- (8CI)
OTHER NAMES:
CN (2,2,6,6-Tetramethyl-1-oxy-4-piperidinyl)amine
CN 2,2,6,6-Tetramethyl-4-amino-1-piperidinyloxy
CN 2,2,6,6-Tetramethyl-4-aminopiperidine N-oxide
CN 2,2,6,6-Tetramethyl-4-aminopiperidine-1-oxyl
CN 4-Amino-2,2,6,6-tetramethyl-1-piperidinyloxy
CN 4-Amino-2,2,6,6-tetramethyl-1-piperidinyloxyl
CN 4-Amino-2,2,6,6-tetramethylpiperidin-1-oxyl
CN 4-Amino-2,2,6,6-tetramethylpiperidine-1-oxy
CN 4-Amino-2,2,6,6-tetramethylpiperidine-N-oxyl
CN 4-Amino-2,2,6,6-tetramethylpiperidino-1-oxy
CN 4-Amino-2,2,6,6-tetramethylpiperidinooxyl
CN 4-Amino-2,2,6,6-tetramethylpiperidinyl-N-oxy
CN 4-Amino-2,2,6,6-tetramethylpiperidinyloxy
CN 4-Aminotempo
CN 6-Tempamine

CN Tempamine
CN Tempo-amine
DR 125342-82-7, 78774-22-8, 26947-98-8
MF C9 H19 N2 O
CI COM
LC STN Files: AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CHEMLIST, CSCHEM, DDFU, DRUGU, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, MEDLINE, TOXLINE, TOXLIT, ULIDAT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



577 REFERENCES IN FILE CA (1967 TO DATE)
42 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
578 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:209532

REFERENCE 2: 133:185450

REFERENCE 3: 133:171762

REFERENCE 4: 133:40243

REFERENCE 5: 133:28209

REFERENCE 6: 133:4597

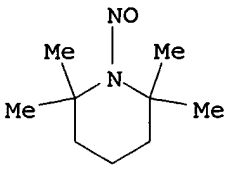
REFERENCE 7: 132:266529

REFERENCE 8: 132:212104

REFERENCE 9: 132:166750

REFERENCE 10: 132:123030

L104 ANSWER 58 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **6130-93-4** REGISTRY
CN Piperidine, 2,2,6,6-tetramethyl-1-nitroso- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1-Nitroso-2,2,6,6-tetramethylpiperidine
CN 2,2,6,6-Tetramethyl-N-nitrosopiperidine
CN 2,2,6,6-Tetramethylnitrosopiperidine
CN N-Nitroso-2,2,6,6-tetramethylpiperidine
FS 3D CONCORD
MF C9 H18 N2 O
CI COM
LC STN Files: BEILSTEIN*, BIOSIS, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, MEDLINE, NIOSHTIC, RTECS*, SPECINFO, TOXLINE, TOXLIT
(*File contains numerically searchable property data)



40 REFERENCES IN FILE CA (1967 TO DATE)
40 REFERENCES IN FILE CAPLUS (1967 TO DATE)
4 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 132:347642

REFERENCE 2: 127:346056

REFERENCE 3: 124:316265

REFERENCE 4: 121:8554

REFERENCE 5: 119:148457

REFERENCE 6: 118:6839

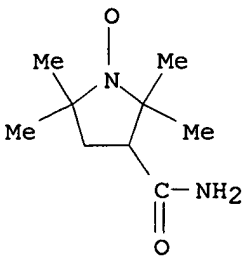
REFERENCE 7: 115:48715

REFERENCE 8: 112:138306

REFERENCE 9: 109:105945

REFERENCE 10: 109:54736

L104 ANSWER 59 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **4399-80-8** REGISTRY
CN 1-Pyrrolidinyloxy, 3-(aminocarbonyl)-2,2,5,5-tetramethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1-Pyrrolidinyloxy, 3-carbamoyl-2,2,5,5-tetramethyl- (7CI, 8CI)
OTHER NAMES:
CN 2,2,5,5-Tetramethyl-3-carbamidopyrrolidine-1-oxyl
CN 2,2,5,5-Tetramethyl-3-carbamoyl-1-pyrrolidinyloxy
CN 2,2,5,5-Tetramethylpyrrolidine-1-oxyl-3-carboxamide
CN 3-Carbamoyl-2,2,5,5-tetramethyl-1-pyrrolidinyloxy
CN 3-Carbamoyl-2,2,5,5-tetramethylpyrrolidine-1-oxyl
CN 3-Carbamoyl-2,2,5,5-tetramethylpyrrolidinooxyl
CN Carbamoyl-PROXYL
CN CPROXYL
CN Proxad
CN T 518
CN Tempamide
DR 55805-96-4
MF C9 H17 N2 O2
CI COM
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CSCHEM, IFICDB, IFIPAT, IFIUDB, MEDLINE, SPECINFO, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



155 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
155 REFERENCES IN FILE CAPLUS (1967 TO DATE)
4 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 133:146947

REFERENCE 2: 133:116965

REFERENCE 3: 133:116940

REFERENCE 4: 133:101589

REFERENCE 5: 133:70746

REFERENCE 6: 133:40243

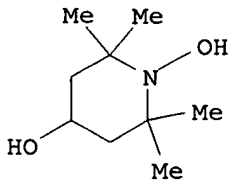
REFERENCE 7: 133:4597

REFERENCE 8: 131:317718

REFERENCE 9: 131:295033

REFERENCE 10: 131:116158

L104 ANSWER 60 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **3637-10-3** REGISTRY
CN 4-Piperidinol, 1-hydroxy-2,2,6,6-tetramethyl- (7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1,4-Dihydroxy-2,2,6,6-tetramethylpiperidine
CN Tempol H
CN TOLH
FS 3D CONCORD
DR 87220-69-7
MF C9 H19 N O2
CI COM
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, DETHERM*, TOXLIT, USPATFULL
(*File contains numerically searchable property data)



75 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
75 REFERENCES IN FILE CAPLUS (1967 TO DATE)

7 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 133:70812

REFERENCE 2: 133:4597

REFERENCE 3: 132:208291

REFERENCE 4: 131:244754

REFERENCE 5: 131:195869

REFERENCE 6: 131:165267

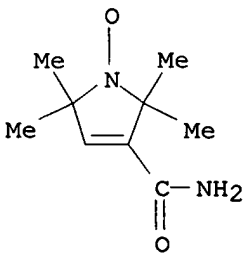
REFERENCE 7: 131:82813

REFERENCE 8: 131:58518

REFERENCE 9: 131:56060

REFERENCE 10: 131:5694

L104 ANSWER 61 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **3229-73-0** REGISTRY
CN 1H-Pyrrol-1-yloxy, 3-(aminocarbonyl)-2,5-dihydro-2,2,5,5-tetramethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Pyrrolin-1-yloxy, 3-carbamoyl-2,2,5,5-tetramethyl- (7CI, 8CI)
OTHER NAMES:
CN 2,2,5,5-Tetramethyl-3-carbamidopyrroline 1-oxyl
CN 3-Carbamoyl-2,2,5,5-tetramethyl-3-pyrrolin-1-yloxy
CN 3-Carbamoyl-2,2,5,5-tetramethyl-3-pyrroline-1-oxyl
CN 3-Carbamoyl-2,2,5,5-tetramethylpyrrolin-1-oxyl
CN CARPYR
CN CTPO
CN Tempyo
DR 35865-16-8
MF C9 H15 N2 O2
LC STN Files: BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, EMBASE, GMELIN*, MEDLINE, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



147 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
147 REFERENCES IN FILE CAPLUS (1967 TO DATE)
9 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 133:174029

REFERENCE 2: 133:131961

REFERENCE 3: 133:40243

REFERENCE 4: 133:30438

REFERENCE 5: 132:113520

REFERENCE 6: 131:243270

REFERENCE 7: 131:124350

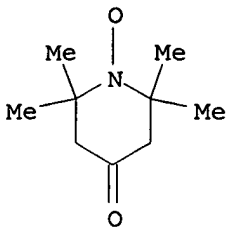
REFERENCE 8: 130:206760

REFERENCE 9: 130:95482

REFERENCE 10: 130:78620

L104 ANSWER 62 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **2896-70-0** REGISTRY
CN 1-Piperidinyloxy, 2,2,6,6-tetramethyl-4-oxo- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Piperidinooxy, 2,2,6,6-tetramethyl-4-oxo- (8CI)
OTHER NAMES:
CN 1-Oxyl-2,2,6,6-tetramethyl-4-piperidone
CN 1-Oxyl-2,2,6,6-tetramethylpiperidin-4-one
CN 2,2,6,6-Tetramethyl-4-oxo-1-piperidinooxy
CN 2,2,6,6-Tetramethyl-4-oxo-1-piperidinyloxy
CN 2,2,6,6-Tetramethyl-4-oxo-1-piperidinyloxyl
CN 2,2,6,6-Tetramethyl-4-oxopiperidin-1-oxyl
CN 2,2,6,6-Tetramethyl-4-oxopiperidine-1-oxyl
CN 2,2,6,6-Tetramethyl-4-oxopiperidine-1-oxyl radical
CN 2,2,6,6-Tetramethyl-4-oxopiperidinooxy
CN 2,2,6,6-Tetramethyl-4-piperidinone-1-oxyl
CN 2,2,6,6-Tetramethyl-4-piperidone 1-nitroxide
CN 2,2,6,6-Tetramethyl-4-piperidone nitroxide
CN 2,2,6,6-Tetramethyl-4-piperidone-N-oxy
CN 2,2,6,6-Tetramethyl-4-piperidone-N-oxyl
CN 2,2,6,6-Tetramethylpiperidone-1-oxyl
CN 4-Oxo-2,2,6,6-tetramethyl-1-piperidinoxyl
CN 4-Oxo-2,2,6,6-tetramethylpiperidine-1-oxyl
CN 4-Oxo-2,2,6,6-tetramethylpiperidino-1-oxy
CN 4-Oxo-2,2,6,6-tetramethylpiperidino-N-oxyl
CN 4-Oxo-2,2,6,6-tetramethylpiperidinooxy
CN 4-Oxo-2,2,6,6-tetramethylpiperidinooxyl
CN 4-Oxo-2,2,6,6-tetramethylpiperidinoxyl
CN 4-Oxo-2,2,6,6-tetramethylpiperidinyl-1-oxy
CN 4-Oxo-2,2,6,6-tetramethylpiperidinyloxy
CN 4-Oxo-TEMPO
CN OTEMPO
CN TAN
CN TAN (radical)
CN TANO
CN Tanone
CN Tanone radical
CN Tempone
CN Triacetoneamine N-oxyl
CN Triacetoneamine nitroxide
DR 70939-26-3, 26841-66-7
MF C9 H16 N O2
CI COM
LC STN Files: AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CSCHEM, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, NIOSHTIC, RTECS*, SPECINFO, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



953 REFERENCES IN FILE CA (1967 TO DATE)
13 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
955 REFERENCES IN FILE CAPLUS (1967 TO DATE)
27 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 133:252852

REFERENCE 2: 133:252363

REFERENCE 3: 133:238802

REFERENCE 4: 133:225262

REFERENCE 5: 133:223565

REFERENCE 6: 133:223166

REFERENCE 7: 133:208647

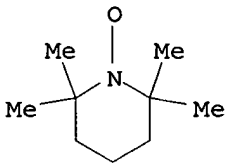
REFERENCE 8: 133:201972

REFERENCE 9: 133:120847

REFERENCE 10: 133:105484

L104 ANSWER 63 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **2564-83-2** REGISTRY
CN 1-Piperidinyloxy, 2,2,6,6-tetramethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Piperidinooxy, 2,2,6,6-tetramethyl- (7CI, 8CI)
OTHER NAMES:
CN 1,1,5,5-Tetramethylpentamethylene nitroxide
CN 1-Oxyl-2,2,6,6-tetramethylpiperidine
CN 2,2',6,6'-Tetramethylpiperidinooxy radical
CN 2,2,6,6-Tetramethyl-1-oxylpiperidine
CN 2,2,6,6-Tetramethyl-1-piperadoxyl
CN 2,2,6,6-Tetramethyl-1-piperidinoxyl
CN 2,2,6,6-Tetramethyl-1-piperidinyloxy
CN 2,2,6,6-Tetramethyl-1-piperidyloxy
CN 2,2,6,6-Tetramethylpiperidin-1-oxy
CN 2,2,6,6-Tetramethylpiperidin-1-oxyl radical
CN 2,2,6,6-Tetramethylpiperidin-N-oxyl
CN 2,2,6,6-Tetramethylpiperidine N-oxide radical
CN 2,2,6,6-Tetramethylpiperidine N-oxy
CN 2,2,6,6-Tetramethylpiperidine N-oxyl
CN 2,2,6,6-Tetramethylpiperidine N-oxyl radical
CN 2,2,6,6-Tetramethylpiperidine nitroxide
CN 2,2,6,6-Tetramethylpiperidine nitroxide radical
CN 2,2,6,6-Tetramethylpiperidine-1-oxyl
CN 2,2,6,6-Tetramethylpiperidino-1-oxy
CN 2,2,6,6-Tetramethylpiperidinooxy
CN 2,2,6,6-Tetramethylpiperidinooxy radical

CN 2,2,6,6-Tetramethylpiperidinooxyl
CN 2,2,6,6-Tetramethylpiperidinoxyl radical
CN 2,2,6,6-Tetramethylpiperidinyl 1-oxide
CN 2,2,6,6-Tetramethylpiperidinyl-1-oxyl
CN 2,2,6,6-Tetramethylpiperidinyl-N-oxy
CN 2,2,6,6-Tetramethylpiperidinyloxy
CN 2,2,6,6-Tetramethylpiperidoxyl
CN HO 6
CN Tanan
CN Tanane
CN Tempo
DR 126517-51-9, 54637-06-8, 125012-91-1, 64104-42-3, 25657-03-8, 26933-82-4
MF C9 H18 N O
CI COM
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, GMELIN*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, NIOSHTIC, PROMT, RTECS*, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



1844 REFERENCES IN FILE CA (1967 TO DATE)
70 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1847 REFERENCES IN FILE CAPLUS (1967 TO DATE)
23 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 133:263239

REFERENCE 2: 133:238852

REFERENCE 3: 133:233780

REFERENCE 4: 133:223138

REFERENCE 5: 133:222166

REFERENCE 6: 133:209532

REFERENCE 7: 133:209514

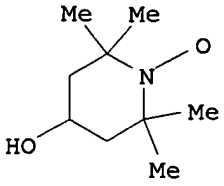
REFERENCE 8: 133:209300

REFERENCE 9: 133:208087

REFERENCE 10: 133:207505

L104 ANSWER 64 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **2226-96-2** REGISTRY
CN 1-Piperidinyloxy, 4-hydroxy-2,2,6,6-tetramethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Piperidinooxy, 4-hydroxy-2,2,6,6-tetramethyl- (7CI, 8CI)
OTHER NAMES:
CN 1-Oxyl-2,2,6,6-tetramethyl-4-hydroxypiperidine
CN 1-Oxyl-2,2,6,6-tetramethyl-4-piperidinol
CN 2,2,6,6-Tetramethyl-4-hydroxy-1-piperidinyloxy radical
CN 2,2,6,6-Tetramethyl-4-hydroxylpiperidine-1-oxyl

CN 2,2,6,6-Tetramethyl-4-hydroxypiperidin-1-oxyl
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidine 1-oxide radical
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidine oxide
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidine-1-oxyl
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidinooxy
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidinooxy radical
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidinyloxy radical
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidinyloxyl radical
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidyl 1-oxyl
CN 2,2,6,6-Tetramethyl-4-oxypiperidine-1-oxyl
CN 2,2,6,6-Tetramethyl-4-piperidinol 1-oxide
CN 2,2,6,6-Tetramethyl-4-piperidinol 1-oxyl
CN 2,2,6,6-Tetramethyl-4-piperidinol N-oxyl
CN 2,2,6,6-Tetramethyl-4-piperidinol nitroxide
CN 2,2,6,6-Tetramethyl-4-piperidinol-1-oxy
CN 2,2,6,6-Tetramethylpiperidine-4-hydroxy-1-oxyl
CN 2,2,6,6-Tetramethylpiperidine-N-oxyl-4-ol
CN 2,2,6,6-Tetramethylpiperidinol-4-oxyl-1
CN 4-Hydroxy-1-oxyl-2,2,6,6-tetramethylpiperidine
CN 4-Hydroxy-2,2,6,6-tetramethyl-1-piperidinoxy
CN 4-Hydroxy-2,2,6,6-tetramethyl-1-piperidinoxyl
CN 4-Hydroxy-2,2,6,6-tetramethyl-1-piperidinyloxy
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidine 1-oxide radical
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidine N-oxide
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidino-1-oxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinooxy
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinooxy radical
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinoxy
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinoxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinyl-1-oxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinyl-N-oxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidyl-1-oxyl
CN 4-hydroxy-TEMPO
CN 4-Oxypiperidol
CN 4H-Tempo
CN HTEMPO
CN HyTEMPO
CN Nitroxyl 2
CN NR I
CN Tanol
CN Tempo OH
CN Tempol
CN TMPN
DR 13075-58-6, 3174-32-1, 105269-77-0, 119227-61-1, 68541-96-8, 70939-25-2, 38854-37-4
MF C9 H18 N O2
CI COM
LC STN Files: ADISINSIGHT, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DETHERM*, DRUGU, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, IMSDIRECTORY, MEDLINE, MSDS-OHS, NIOSHTIC, PIRA, RTECS*, TOXLINE, TOXLIT, ULIDAT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



1641 REFERENCES IN FILE CA (1967 TO DATE)
41 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1642 REFERENCES IN FILE CAPLUS (1967 TO DATE)
24 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 133:253292

REFERENCE 2: 133:233780

REFERENCE 3: 133:223565

REFERENCE 4: 133:223171

REFERENCE 5: 133:223166

REFERENCE 6: 133:223108

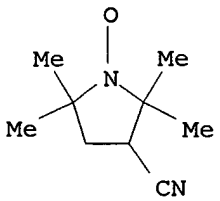
REFERENCE 7: 133:222595

REFERENCE 8: 133:222194

REFERENCE 9: 133:209532

REFERENCE 10: 133:208304

L104 ANSWER 65 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **2154-70-3** REGISTRY
CN 1-Pyrrolidinyloxy, 3-cyano-2,2,5,5-tetramethyl- (7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN 3-Cyano-2,2,5,5-tetramethylpyrrolidine-N-oxyl
MF C9 H15 N2 O
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, CHEMCATS, MEDLINE, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)



12 REFERENCES IN FILE CA (1967 TO DATE)
12 REFERENCES IN FILE CAPLUS (1967 TO DATE)
3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 131:45141

REFERENCE 2: 130:68047

REFERENCE 3: 130:26383

REFERENCE 4: 128:267962

REFERENCE 5: 128:158896

REFERENCE 6: 127:217088

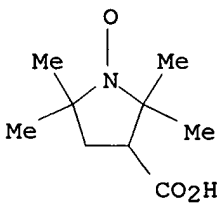
REFERENCE 7: 126:82020

REFERENCE 8: 122:9868

REFERENCE 9: 117:229205

REFERENCE 10: 114:185185

L104 ANSWER 66 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **2154-68-9** REGISTRY
CN 1-Pyrrolidinyloxy, 3-carboxy-2,2,5,5-tetramethyl- (7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2,2,5,5-Tetramethyl-3-carboxypyrrolidine-N-oxyl
CN 2,2,5,5-Tetramethyl-3-carboxypyrrolidinooxy
CN 2,2,5,5-Tetramethylpiperidine-1-oxyl-3-carboxylic acid
CN 2,2,5,5-Tetramethylpyrrolidine-1-oxyl-3-carboxylic acid
CN 3-Carboxy-2,2,5,5-tetramethyl-1-pyrrolidinyloxy
CN 3-Carboxy-2,2,5,5-tetramethylpyrrolidinyloxyl
CN DL-3-Carboxy-2,2,5,5-tetramethyl-1-pyrrolidinyloxyl
CN PCA
CN PCA (radical)
CN T 517
DR 56048-07-8, 68398-73-2
MF C9 H16 N O3
CI COM
LC STN Files: AGRICOLA, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CSCHEM, EMBASE, IFICDB, IFIPAT, IFIUDB, MEDLINE, RTECS*, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



216 REFERENCES IN FILE CA (1967 TO DATE)
8 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
216 REFERENCES IN FILE CAPLUS (1967 TO DATE)
3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 133:109811

REFERENCE 2: 133:70813

REFERENCE 3: 133:40243

REFERENCE 4: 132:265597

REFERENCE 5: 132:248541

REFERENCE 6: 132:237544

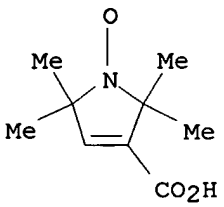
REFERENCE 7: 132:151870

REFERENCE 8: 131:337278

REFERENCE 9: 131:258046

REFERENCE 10: 131:70664

L104 ANSWER 67 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **2154-67-8** REGISTRY
CN 1H-Pyrrol-1-yloxy, 3-carboxy-2,5-dihydro-2,2,5,5-tetramethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Pyrrolin-1-yloxy, 3-carboxy-2,2,5,5-tetramethyl- (7CI, 8CI)
OTHER NAMES:
CN 2,2,5,5-Tetramethyl-1-oxypyrroline-3-carboxylic acid
CN PCAOL
DR 109871-95-6
MF C9 H14 N O3
CI COM
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CSCHEM, MEDLINE, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



144 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
144 REFERENCES IN FILE CAPLUS (1967 TO DATE)
4 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 133:222926

REFERENCE 2: 133:13592

REFERENCE 3: 131:243270

REFERENCE 4: 131:19259

REFERENCE 5: 129:254346

REFERENCE 6: 128:248580

REFERENCE 7: 128:97775

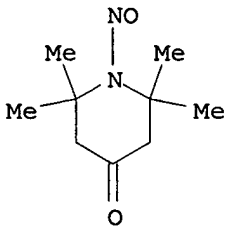
REFERENCE 8: 128:34599

REFERENCE 9: 127:144745

REFERENCE 10: 127:95594

L104 ANSWER 68 OF 68 REGISTRY COPYRIGHT 2000 ACS
RN **640-01-7** REGISTRY
CN 4-Piperidinone, 2,2,6,6-tetramethyl-1-nitroso- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:
CN 4-Piperidone, 2,2,6,6-tetramethyl-1-nitroso- (6CI, 7CI)
FS 3D CONCORD
MF C9 H16 N2 O2
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, IFICDB, IFIPAT, IFIUDB, SPECINFO, TOXLINE, TOXLIT
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)



7 REFERENCES IN FILE CA (1967 TO DATE)
7 REFERENCES IN FILE CAPLUS (1967 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 110:90363

REFERENCE 2: 106:138223

REFERENCE 3: 98:197964

REFERENCE 4: 93:168077

REFERENCE 5: 90:86151

REFERENCE 6: 88:59209

REFERENCE 7: 80:134246

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 11:18:00 ON 28 OCT 2000
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1967 - 28 Oct 2000 VOL 133 ISS 19
FILE LAST UPDATED: 27 Oct 2000 (20001027/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REGlstRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

Now you can extend your author, patent assignee, patent information, and title searches back to 1907. The records from 1907-1966 now have this searchable data in CAOLD. You now have electronic access to all

of CA: 1907 to 1966 in CAOLD and 1967 to the present in HCAPLUS on STN.

=> d bib abs hitrn tot l103

L103 ANSWER 1 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 2000:720111 HCAPLUS
TI The **nitroxide tempol** induces oxidative stress, p21WAF1/CIP1, and cell death in HL60 cells
AU Gariboldi, M. B.; Rimoldi, V.; Supino, R.; Favini, E.; Monti, E.
CS Section of Pharmacology, Varese, University of Insubria, Department of Structural and Functional Biology, Milan, Italy
SO Free Radical Biol. Med. (2000), 29(7), 633-641
CODEN: FRBMEH; ISSN: 0891-5849
PB Elsevier Science Inc.
DT Journal
LA English
AB The antiproliferative effect of **Tempol**, a stable **nitroxide** free radical, was investigated on the **p53**-neg. human leukemia cell line HL60. A concn.- and time-dependent inhibition of cell growth was obsd. that appears to be due to induction of apoptosis. Involvement of oxidative stress is indicated by a concn.-dependent increase in intracellular peroxides and a parallel decrease in total cellular glutathione; in addn., increased survival rates were obsd. in cells simultaneously treated with **Tempol** and the antioxidant N-acetylcysteine. **Tempol** did not affect the relative levels of Bax and Bcl2, whereas p21WAF1/CIP1 was enhanced in a concn.- and time-dependent fashion; this effect was partially inhibited by N-acetylcysteine, was maintained for up to 8 h after **Tempol** removal, and seemed to depend on continuing protein synthesis. The increase in p21WAF1/CIP1 was accompanied by a parallel accumulation of cells in the G1 phase of the cycle and by a decrease in the 110 kDa form of pRb. Our results suggest that **p53**-independent induction of p21WAF1/CIP1 mediates the antiproliferative effect of **Tempol**; on the basis of this observation, the **nitroxide** could be proposed as an useful adjunct to the treatment of **p53**-deficient tumors, which are often refractory to std. chemotherapy.

L103 ANSWER 2 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:800011 HCAPLUS
DN 130:20564
TI The use of a **nitroxide** or a prodrug thereof in the prophylactic and therapeutic treatment of **cancer**
IN **Mitchell, James B.; Russo, Angelo; Deluca, Anne Marie; Cherukuri, Murali Krishna**
PA United States Dept. of Health and Human Services, USA
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI WO 9853835	A1	19981203	WO 1998-US10685	19980527	<--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
AU 9875987	A1	19981230	AU 1998-75987	19980527	<--
EP 986393	A1	20000322	EP 1998-923772	19980527	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,					

IE, FI
PRAI US 1997-47724 19970527 <--
WO 1998-US10685 19980527
OS MARPAT 130:20564
AB A method is provided for the prophylactic and therapeutic treatment of **cancer**. The method comprises administering to an animal, preferably a mammal, more preferably a human, at risk for developing a **cancer** or having a **cancer** a **nitroxide** or a prodrug thereof, wherein the **nitroxide** or prodrug thereof, preferably alicyclic or heterocyclic (Markush included), in an amt. sufficient to prevent or treat the **cancer**, wherein the **cancer** is susceptible to prevention or treatment by the **nitroxide** or prodrug thereof. Also provided is a compn. for use in the method.
IT **2226-96-2, Tempol**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**nitroxide** or prodrug thereof for **cancer** treatment)
RE.CNT 4
RE
(1) Monti; PAACR ANNUAL MEETING 1977, V38(0), P193
(2) Monti; PAACR ANNUAL MEETING 1995, V36(0), P387
(3) Monti; PAACR ANNUAL MEETING 1998, V39(0), P90
(4) Us Government; WO 9640127 A 1996

L103 ANSWER 3 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:607266 HCAPLUS
DN 127:287857
TI **Tempol** inhibits neutrophil and hydrogen peroxide-mediated DNA damage
AU Hahn, Stephen M.; **Mitchell, James B.**; Shacter, Emily
CS Radiation Biology Branch, Division of Clinical Sciences, National Cancer Institute, Bethesda, MD, 20892, USA
SO Free Radical Biol. Med. (**1997**), 23(6), 879-884
CODEN: FRBMEH; ISSN: 0891-5849
PB Elsevier
DT Journal
LA English
AB Inflammatory conditions characterized by neutrophil activation are assocd. with a variety of chronic diseases. Reactive oxygen species are produced by activated neutrophils and produce DNA damage which may lead to tissue damage. Previous studies have shown that activated murine neutrophils induce DNA strand breaks in a target plasmacytoma cell, RIMPC 2394. We studied the effect of a water sol. **nitroxide** antioxidant, **Tempol**, on murine neutrophil induction of DNA strand breaks in this system. Murine neutrophils were isolated from the peritoneal cavity of BALB/cAn mice after an IP injection of pristane oil. Neutrophils were activated by the phorbol ester PMA and co-incubated with RIMPC 2394 cells. Control alk. elution studies revealed progressive DNA strand breaks in RIMPC cells with time. The addn. of **Tempol** to the incubation mixt. prevented DNA damage in a dose dependent fashion. Five mM **Tempol** provided complete protection. **Tempol** protection against DNA strand breaks was similar for both stimulated neutrophils and exogenously added hydrogen peroxide. Measurement of hydrogen peroxide produced by stimulated neutrophils demonstrated that **Tempol** did not decrease hydrogen peroxide concn. Oxidn. of reduced metals, thereby interfering with the prodn. of hydroxyl radical, is the most likely mechanism of **nitroxide** protection, although superoxide dismutase (SOD)-like activity and scavenging of carbon-based free radicals may also account for a portion of the obsd. protection. The antioxidant activity of **Tempol** inhibited DNA damage by activated neutrophils. The **nitroxides** as a class of compds. may have a role in the investigation and modification of inflammatory conditions.
IT **2226-96-2, Tempol**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**tempol** inhibits neutrophil and hydrogen peroxide-mediated DNA damage)

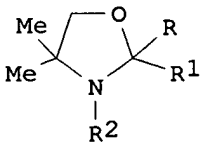
L103 ANSWER 4 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:596212 HCAPLUS
DN 127:256948
TI Antioxidant properties of **nitroxides** and **nitroxide** SOD mimics
AU Samuni, Amram; **Krishna, Murali C.**
CS Department of Molecular Biology, Hebrew University Medical School, Jerusalem, Israel
SO Antioxid. Health Dis. (**1997**), 4(Handbook of Synthetic Antioxidants), 351-373
CODEN: AHDIEQ
PB Dekker
DT Journal; General Review
LA English
AB A review with 86 refs. of possible use of **nitroxides** and **nitroxide** SOD mimics as neuroprotectants.

L103 ANSWER 5 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:258309 HCAPLUS
DN 126:290156
TI Evaluation of **tempol** radioprotection in a murine **tumor** model
AU Hahn, Stephen M.; Sullivan, Francis J.; **DeLuca, Anne Marie; Krishna, C. Murali;** Wersto, Nancy; Venzon, David; **Russo, Angelo; Mitchell, James B.**
CS Radiation Biol. Branch, Natl. Cancer Inst., Bethesda, MD, USA
SO Free Radical Biol. Med. (**1997**), 22(7), 1211-1216
CODEN: FRBMEH; ISSN: 0891-5849
PB Elsevier
DT Journal
LA English
AB **Tempol**, a stable **nitroxide** free radical compd., is an in vitro and in vivo radioprotector. Previous studies have shown that **Tempol** protects C3H mice against whole-body radiation-induced bone marrow failure. In this study, the radioprotection of **tumor** tissue was evaluated. RIF-1 **tumor** cells were implanted in female C3H mice 10 d prior to radiation. Groups of mice were injected i.p. with **Tempol** (275 mg/kg) or PBS followed 10 min later by a single dose of radiation to the **tumor** bed. **Tumor** growth curves generated after 10 and 33.3 Gy doses of radiation showed no difference in growth between the **Tempol**- and PBS-treated animals. A full radiation dose-response expt. revealed a **tumor** control dose in 50% of the animals in 30 d(TCD50/30) value of 36.7 Gy for **Tempol**-treated mice and 41.8 Gy for saline-treated mice suggesting no protection of the RIF-1 **tumor** by **Tempol**. **Tumor** pharmacokinetics were done to det. why **Tempol** differentially protected bone marrow and not **tumor** cells. Differential redn. of **Tempol** in the RIF-1 **tumor** and bone marrow was evaluated with EPR spectroscopy 10, 20, and 30 min after injection. Bioredn. of **Tempol** to its corresponding hydroxylamine (which is not a radioprotector) occurred to a greater extent in RIF-1 **tumor** cells compared to bone marrow. We conclude that the differences in radioprotection may result from enhanced **intratumor** bioredn. of **Tempol** to its nonradioprotective hydroxylamine analog. The **nitroxides** as a class of compds. may provide a means to exploit the redox differences between normal tissues and **tumors**.
IT **2226-96-2, Tempol**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**tempol** radioprotection evaluation in murine **tumor** model)

L103 ANSWER 6 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:140234 HCAPLUS
DN 126:139898
TI **Nitroxides** as protectors against oxidative stress
IN **Mitchell, James B.**; Samuni, Amran; Degraff, William G.; Hahn, Stephen
PA United States Dept. of Health and Human Services, USA
SO PCT Int. Appl., 50 pp
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9640127	A1	19961219	WO 1996-US9524	19960607 <--
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML				
AU 9661028	A1	19961230	AU 1996-61028	19960607 <--
PRAI US 1995-473960	19950607 <--			
WO 1996-US9524	19960607 <--			

OS MARPAT 126:139898
GI



I

AB The instant invention is directed to the use of a biol. compatible compn., contg. an effective amt. of a metal-independent **nitroxide** compd. which is preferably represented by formula (I), wherein R is -CH3; R1 is -C2H5, -C3H7, -C4H9, -C5H11, -C6H13, -CH2-CH(CH3)2, -CHCH3C2H5 or -(CH2)7-CH3, or where R and R1 together form spirocyclopentane, spirocyclohexane, spirocycloheptane, spirocyclooctane, 5-cholestane, or norbornane, R2 is -O., or -OH, or a physiol. acceptable salt thereof, and a pharmaceutically acceptable carrier, as antioxidants capable of protecting cells, tissues, organs, and whole organs against the deleterious effects of harmful free radical species generated during oxidative stress.

IT **16263-51-7P 16302-61-7P 35203-77-1P**
35328-03-1P 35328-06-4P 35328-08-6P
63035-93-8P 65162-38-1P, Oxano **75164-94-2P**
125569-48-4P 174153-11-8P 186664-89-1P
186664-90-4P 186664-91-5P 186664-92-6P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and formulation of **nitroxides** as protectors against oxidative stress)

IT **2226-96-2, TEMPOL 2564-83-2, TEMPO**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. and formulation of **nitroxides** as protectors against oxidative stress)

L103 ANSWER 7 OF 57 HCAPLUS COPYRIGHT 2000 ACS

AN 1997:92226 HCAPLUS
DN 126:166187
TI Protection of mitomycin C-induced skin extravasation with the **nitroxide**, 3-carbamoyl-PROXYL (3-CP)
AU Hahn, Stephen M.; Sullivan, Frank J.; **De Luca, Anne Marie**; Sprague, Merle; Hampshire, Victoria A.; **Krishna, Murali C.**; **Russo, Angelo**; **Mitchell, James B.**
CS Radiation Biology Branch, Division of Clinical Sciences, National Cancer Institute, Bethesda, MD, 20892, USA
SO Int. J. Oncol. (**1997**), 10(1), 119-123
CODEN: IJONES; ISSN: 1019-6439
PB International Journal of Oncology
DT Journal
LA English
AB Extravasation tissue injury from chemotherapeutic drugs is a serious clin. problem. A swine model has been useful for studying skin extravasation and evaluating potential antidotes. Mitomycin C (MMC) skin extravasation was studied. **Nitroxides**, a class of compds. which are protective against a variety of oxidative stresses in vitro, including MMC, were tested as antidotes. Miniature swine were anesthetized and given intradermal (ID) injections of MMC. MMC alone caused skin necrosis and ulceration. Several **nitroxides** were screened as protectors of MMC-induced skin necrosis. 3-Carbamoyl-PROXYL (3-CP) was the lone **nitroxide** which protected if given 5 min after extravasation. Administration of 3-CP 10 min after MMC injection was not protective. In vitro studies with monolayered V79 cells showed that 3-CP had a direct protective effect against MMC **cytotoxicity** in a concn.-dependent fashion. Therefore, in the swine model doses of 3-CP ranging from 25-100 mM were tested and found to protect against MMC skin necrosis 90 days after injection. Histol. sections of the 3-CP- and MMC-treated pig skin showed a marked redn. in the degree of acute inflammation and the absence of deep dermal scarring when compared to MMC alone.
IT **4399-80-8**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(protection of mitomycin C-induced skin extravasation with the **nitroxide**, 3-carbamoyl-PROXYL (3-CP))

L103 ANSWER 8 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:86858 HCAPLUS
DN 126:195017
TI Direct evidence for in vivo **nitroxide** free radical production from a new antiarrhythmic drug by EPR spectroscopy
AU Twomey, Patrick; Taira, Junsei; Degraff, William; **Mitchell, James B.**; **Russo, Angelo**; **Krishna, Murali C.**; Hankovszky, Olga H.; Frank, Laszlo; Hideg, Kalman
CS Radiation Biology Branch, National Cancer Institute, NIH, Bethesda, MD, 20892, USA
SO Free Radical Biol. Med. (**1997**), 22(5), 909-916
CODEN: FRBMEH; ISSN: 0891-5849
PB Elsevier
DT Journal
LA English
AB The new Class I anti-arrhythmic agent, 2,2,5,5-tetramethyl-3-pyrroline-1-carboxamide deriv., is currently being evaluated in clin. trials in patients with a high risk for cardiac arrhythmias. In this study the authors show that this antiarrhythmic drug can be chem. converted to the **nitroxide** free radical analog. Further, using an in vivo ESR (EPR) spectroscopy model by detecting free radicals in the distal portion of the tail of an anesthetized mouse, the authors demonstrate that the drug is oxidized to the corresponding **nitroxide**. In vitro studies using Chinese hamster V79 cells suggest that the oxidn. products of the drug, namely, the hydroxylamine and the **nitroxide** protect against oxidative damage induced by hydrogen peroxide (H2O2). Taken together, our results suggest that, in addn. to the antiarrhythmic effects of the parent drug, sufficient levels of **nitroxides** may

accumulate from the parent drug in vivo to provide antioxidant defense to cardiac tissue that may be subject to ischemia and oxidn.-driven injury.

IT **102132-45-6 102132-51-4**
RL: BAC (Biological activity or effector, except adverse); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)
(in vivo **nitroxide** free radical prodn. from new antiarrhythmic drug and antioxidant activities in mice)

IT **93799-37-2**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vivo **nitroxide** free radical prodn. from new antiarrhythmic drug and antioxidant activities in mice)

L103 ANSWER 9 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:644233 HCAPLUS
DN 125:317237
TI Do **nitroxide** antioxidants act as scavengers of superoxide radical or as SOD mimics?
AU **Krishna, Murali C.**; **Russo, Angelo**; **Mitchell, James B.**; Goldstein, Sara; Dafni, Hagit; Samuni, Amram
CS Molecular Biolog, Hebrew Univ., Jerusalem, 91120, Israel
SO J. Biol. Chem. (**1996**), 271(42), 26026-26031
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Stable **nitroxide** radicals were reported to act as SOD mimics and catalyze the **dismutation** of superoxide radical through two different catalytic pathways including reductive and oxidative reaction mechanisms. Recent studies directly monitoring superoxide radical and employing kinetics anal. did not reveal SOD activity of **nitroxides**. Such discrepancy may result in cases where distinction of stoichiometric scavengers from catalytic detoxifiers of superoxide radical is not readily feasible. **Nitroxides** are effective antioxidants that protect against oxidative injury in various pathol. processes. The distinction of their SOD mimic activity from superoxide radical scavenging was established by examg. the validity of direct and indirect methods employed to assay SOD-like catalytic activity. Kinetics anal. along with direct EPR monitoring were used to study the mechanism underlying **nitroxide** reactions with superoxide radical. The **nitroxide** EPR signal decayed in the presence of NADH but otherwise did not decrease with time, thus substantiating its catalytic role in superoxide radical **dismutation**. The catalytic rate consts. for superoxide radical **dismutation**, detd. for the **nitroxides** tested, were found to increase with [H+], indicating that .bul.OOH rather than superoxide radical is oxidizing the **nitroxide**. The results demonstrate the limitations assocd. with direct kinetics anal. in evaluating SOD mimic activity, underscoring the need for independent assays for valid discrimination of SOD mimics from stoichiometric scavengers of superoxide radical.

IT **2226-96-2**, 4-Hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl
2564-83-2, 2,2,6,6-Tetramethylpiperidine-1-oxyl
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**nitroxide** antioxidants as scavengers of superoxide radical or as SOD mimics)

L103 ANSWER 10 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:644232 HCAPLUS
DN 125:295936
TI Stimulation by **nitroxides** of catalase-like activity of hemeproteins. Kinetics and mechanism
AU **Krishna, Murali C.**; Samuni, Amram; Taira, Junsei; Goldstein, Sara; **Mitchell, James B.**; **Russo, Angelo**
CS Radiation Biology Branch, National Institutes of Health, Bethesda, MD, 20892, USA
SO J. Biol. Chem. (**1996**), 271(42), 26018-26025

CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB The ability of stable **nitroxide** radicals to detoxify hypervalent heme proteins such as ferrylmyoglobin (MbFeIV) produced in the reaction of metmyoglobin (MbFeIII) and H2O2 was evaluated by monitoring O2 evolution, H2O2 depletion, and redox changes of the heme prosthetic group. The rate of H2O2 depletion and O2 evolution catalyzed by MbFeIII was enhanced by stable **nitroxides** such as 4-OH-2,2,6,6-tetramethyl-piperidinoxyl (TPL) in a catalytic fashion. The redn. of MbFeIV to MbFeIII enhanced catalase-like activity more than 4-fold. During **dismutation** of H2O2, [TPL] and [MgFeIV] remained const. NADH caused: (a) inhibition of H2O2 decay; (b) progressive redn. of TPL to its resp. hydroxylamine TPL-H; and (c) arrest/inhibition of oxygen evolution or elicit consumption of O2. Following depletion of NADH the evolution of O2 resumed and the initial concn. of TPL was restored. Kinetic anal. showed that two distinct forms of MbFeIV might be involved in the process. In summary, by shuttling between two oxidn. states, namely **nitroxide** and oxoammonium cation, stable **nitroxides** enhance the catalase mimic activity of MbFeIII, thus facilitating H2O2 **dismutation** accompanied by O2 evolution and providing protection against hypervalent heme proteins.
IT **2226-96-2**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(stimulation by **nitroxides** of catalase-like activity of hemeproteins. Kinetics and mechanism)

L103 ANSWER 11 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:258683 HCAPLUS
DN 124:332440
TI Hydroxyurea reacts with heme proteins to generate nitric oxide
AU Pacelli, R.; Taira, J.; Cook, J. A.; Wink, D. A.; **Krishna, M. C.**
CS NCI, NIH, Bethesda, MD, 20892, USA
SO Lancet (**1996**), 347(9005), 900
CODEN: LANCAO; ISSN: 0140-6736
DT Journal
LA English
AB Simulating in vitro the oxidative metab. of hydroxyurea in the presence of heme proteins and hydrogen peroxide, the authors found by a colorimetric method (Griess assay), accumulation of nitrites, indicative of nitric oxide (NO) generation from hydroxyurea. By ESR spectroscopy (EPR), the authors obsd. the generation of a **nitroxide** radical from hydroxyurea which further decompd. to produce NO which could be trapped by the NO specific spin-trap agent carboxy-PTIO and detected by EPR. The generation of NO from hydroxyurea may have implications in its pharmacol., esp. in the treatment of sickle cell anemia.

L103 ANSWER 12 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:979402 HCAPLUS
DN 124:83285
TI New directions for free radical **cancer** research and medical applications
AU Hahn, Stephen M.; **Krishna, C. Murali; Mitchell, James B.**
CS National Cancer Institute, National Institutes Health, Bethesda, MD, 20892, USA
SO Adv. Exp. Med. Biol. (**1994**), 366(Free Radicals in Diagnostic Medicine), 241-51
CODEN: AEMBAP; ISSN: 0065-2598
DT Journal; General Review
LA English
AB A review with 36 refs. The development of a class of anti-oxidant compds., the **nitroxides**, which highlight many of the features of free radicals as they pertain to **cancer** research is described.

L103 ANSWER 13 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:586969 HCAPLUS

DN 123:78627
TI Protection from radiation-induced chromosomal aberrations by the **nitroxide Tempol**
AU Johnstone, Peter A. S.; DeGraff, William G.; **Mitchell, James B.**
CS Radiation Biology Branch, National Cancer Institute, Bethesda, MD, USA
SO Cancer (Philadelphia) (**1995**), 75(9), 2323-7
CODEN: CANCAR; ISSN: 0008-543X
DT Journal
LA English
AB The **nitroxide Tempol** (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl) is a stable, free radical that exhibits protection from ionizing radiation damage and from oxidative stress mediated through exposure of cells to superoxide or hydrogen peroxide. Radiation protection has been obsd. in both in vivo and in vitro models. To understand the mechanism of **Tempol**-mediated radioprotection better, the prodn. of radiation induced chromosome aberrations was evaluated. This study analyzed **Tempol**-mediated radioprotection of human peripheral blood lymphocytes (PBLs). Peripheral blood lymphocytes were exposed to control (0mM), 10 mM (Tp10), and 50 mM (Tp50) concns. of **Tempol** for 20 min before irradn. with 0, 150, 300, and 450 cGy. One quarter mL whole blood was cultured in F12 medium and phytohemagglutinin at 37.degree. for 49, 54, 59, and 64 h. Colcemid was added to each sample for the last 5 h before harvest. Cells were harvested, treated with hypotonic soln., and fixed before dropping on cold clean slides. Mitotic indexes and frequency of dicentric, ring, and triradial chromosomal aberrations were detd. at 1000.times. magnification for each treatment group at each collection point. Treatment of cells with **Tempol** alone did not induce the chromosomal aberration frequency above that for unirradiated controls. Radiation dose response curves for total chromosome aberration prodn. revealed radioprotection for **Tempol** treatment for both 10 and 50 mM exposures. **Tempol** protection factors (assessed at 0.2 aberrations/cell level) for Tp 10 and Tp 50 were 2.2 and 2.8, resp. **Tempol** protects against radiation-induced chromosome aberrations in human PBLs. This finding is consistent with and lends support to previous studies in which **Tempol** was reported to enhance cell survival and reduce radiation-induced DNA double strand breaks.
IT **2226-96-2, Tempol**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(protection from radiation-induced chromosomal aberrations by **nitroxide Tempol**)

L103 ANSWER 14 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:584888 HCAPLUS
DN 123:4740
TI Neurophysiological consequences of **nitroxide** antioxidants
AU Hahn, Stephen M.; Lepinski, Dennis L.; **DeLuca, Anne Marie**; **Mitchell, James B.**; Pellmar, Terry C.
CS Div. Cancer Treatment, Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Can. J. Physiol. Pharmacol. (**1995**), 73(3), 399-403
CODEN: CJPPA3; ISSN: 0008-4212
DT Journal
LA English
AB **Nitroxides** are antioxidant compds. that have been shown to provide radioprotection in vivo and in vitro. Radioprotection in vivo is limited by toxicity, which appears to be neurol. in nature. To further evaluate the toxicity of these compds., 3 representative **nitroxides**: **Tempol**, Tempamine, and **Tempo**, were examd. in slices of guinea pig hippocampus. Each **nitroxide** increased the population spike and potentiated excitatory postsynaptic potential-spike coupling. Repetitive activity and epileptiform activity were obsd. at the highest concns. of **Tempo** and Tempamine used. **Tempol** was the least toxic compd. in this system, followed by Tempamine and **Tempo**.
IT **2226-96-2, Tempol 2564-83-2, Tempo**

14691-88-4, Tempamine
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(neurophysiol. effects of **nitroxide** antioxidants)

L103 ANSWER 15 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:197635 HCAPLUS
DN 122:1002
TI **Nitroxides** as antioxidants
AU **Krishna, Murali C.**; Samuni, Amram
CS Radiat. Oncol. Branch, Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Methods Enzymol. (**1994**), 234(Oxygen Radicals in Biological Systems, Pt. D), 580-9
CODEN: MENZAU; ISSN: 0076-6879
DT Journal
LA English
AB Procedures adopted for applying and assaying the antioxidant activity of **nitroxides** are presented.

L103 ANSWER 16 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:671515 HCAPLUS
DN 121:271515
TI Free radical modes of **cytotoxicity** of Adriamycin and streptonigrin
AU DeGraff, William; Hahn, Stephen M.; **Mitchell, J. B.**; **Krishna, Murali**
CS Radiation Biology Branch, National Inst. of Health, Bethesda, MD, 20892, USA
SO Biochem. Pharmacol. (**1994**), 48(7), 1427-35
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English
AB Free radical modes of **cytotoxicity** of streptonigrin (STN) and Adriamycin (ADR) in Chinese hamster V79 cells under aerobic conditions were evaluated using 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (TP), a low mol. wt. stable **nitroxide** free radical with antioxidant properties and desferrioxamine (DF), a transition metal chelator. In addn., exogenous superoxide dismutase (SOD, EC 1.15.1.1) and catalase (CAT, EC1.11.1.6), were tested for cytoprotective effects. EPR studies showed that TP reacts with the semiquinones of both ADR and STN and also with O2- radicals generated during aerobic redox cycling of the resp. semiquinone radicals. Pulsed field gel electrophoresis studies confirmed that DNA double-strand breaks (dsb) induced by STN in V79 cells were inhibited completely by TP, whereas ADR-induced DNA dsb were not affected by TP. Clonogenic cell survival studies showed that STN-induced **cytotoxicity** could be inhibited completely by DF or TP. Both agents were ineffective in inhibiting ADR-induced **cytotoxicity**. SOD and CAT were ineffective in protecting against both STN and ADR **cytotoxicity**. Our results are consistent with a mechanism requiring the semiquinone radical intermediate of STN for **cytotoxicity** and minimal free radical involvement in ADR-induced V79 cell **cytotoxicity**.

L103 ANSWER 17 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:671477 HCAPLUS
DN 121:271477
TI Modulation of streptonigrin **cytotoxicity** by **nitroxide** SOD mimics
AU **Krishna, Murali C.**; Halevy, Rivka F.; Zhang, Renliang; Gutierrez, Peter L.; Samuni, Amram
CS National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
SO Free Radical Biol. Med. (**1994**), 17(5), 379-88
CODEN: FRBMEH; ISSN: 0891-5849
DT Journal
LA English
AB **Nitroxides** are cell-permeable, stable radicals that react

readily with paramagnetic species such as transition metals or short-lived free radicals, though not generally with diamagnetic mols. **Nitroxides** can undergo one-electron selective redox reactions and thereby potentially modify the activity of **cytotoxic** drugs. Streptonigrin (SN) toxicity requires bioredn. to yield the semiquinone radical, and the toxicity is reportedly mediated by transition metals and oxygen-derived reactive species via redox-cycling of the semiquinone intermediate. The present study shows that (1) **nitroxides** protected isolated DNA and also aerated or hypoxic bacterial cells from SN toxicity; (2) H2O2 potentiated the hypoxic **cytotoxicity** of the drug but inhibited the damage to aerated cells; (3) pretreatment of cells with H2O2 conferred some protection, but not when the drug alone was pre-exposed to H2O2; and (4) desferrioxamine and 2,2-dipyridyl, though neither diethylenetriamino pentaacetate, exogenous catalase, or superoxide dismutase, decreased SN-induced cell killing. The mechanisms by which **nitroxides** protect from SN toxicity involve both a selective radical-radical reaction with SN semiquinone and the reoxidn. of reduced cellular transition metal ions. On the other hand, H2O2 appears to exert two opposing effects: (1) facilitation of cell killing by the Fenton reaction and (2) lowering the cellular level of reducing equiv., thus inhibiting the bioreductive activation of SN.

L103 ANSWER 18 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:595140 HCAPLUS
DN 121:195140
TI Bioreductive metabolism of SR-4233 (WIN 59075) by whole cell suspensions under aerobic and hypoxic conditions: role of the pentose cycle and implications for the mechanism of **cytotoxicity** observed in air
AU Tuttle, Stephen W.; Hazard, Lisa; Koch, Cameron J.; **Mitchell, James B.**; Coleman, C. Norman; Biaglow, John E.
CS Sch. Med., Univ. Pennsylvania, Philadelphia, PA, USA
SO Int. J. Radiat. Oncol., Biol., Phys. (**1994**), 29(2), 357-62
CODEN: IOBPD3; ISSN: 0360-3016
DT Journal
LA English
AB Measurement of pentose cycle (PC) activity is shown to be a noninvasive means for monitoring the redn. of SR-4233 in whole cells. Comparing these measurements to the actual measurements of drug loss under aerobic and hypoxic conditions helps to define the mechanism for the assocd. aerobic toxicity. SR-4233 is activated to a toxic species by bioreductive metab. NADPH is required for the activation of the drug by purified enzymes, cell homogenates and whole cells. In vivo the NADPH:NADP+ ratio is maintained by the oxidn. of glucose via the oxidative limb of the PC. By measuring radiolabeled 14CO2 released as a product of this oxidn., one can get an accurate measurement of the rate of drug metab. in whole cells. These results are compared to measurements of drug consumption under aerobic and hypoxic conditions using an HPLC assay. SR-4233 stimulates PC activity to a greater extent in air then under hypoxia; however, in the presence of added catalase, PC activity is stimulated to a similar extent under both conditions. The higher levels of PC activity obsd. in air are due to the prodn. of hydrogen peroxide by the **nitroxide** free radical undergoing futile redox cycling. The contribution of H2O2 to the obsd. aerobic **cytotoxicity** of SR-4233 is minimal however, since toxicity is only slightly reduced in the presence of exogenous catalase and antioxidants such as vitamin E. The level of PC stimulation by SR-4233 suggests that the rate of electron addn. to the drug is independent of O2 concn. The loss of drug from the incubation medium, i.e., conversion to a stable intermediate species, occurs approx. five times faster under nitrogen than in air for A549 cells. It is the rate of drug loss from the cell and not the rate of redn. which best correlates with the obsd. aerobic and hypoxic toxicity. Toxicity in air and in nitrogen is directly related to the rate of drug redn.; i.e., at equiv. levels of drug loss, we observe equal levels of **cytotoxicity**.

L103 ANSWER 19 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:579003 HCAPLUS

DN 121:179003
TI Novel DMPO-Derived 13C-Labeled Spin Traps Yield Identifiable Stable **Nitroxides**
AU Barasch, Dinorah; **Krishna, Murali C.**; **Russo, Angelo**; Katzhendler, Jehoshua; Samuni, Amram
CS School of Medicine and Pharmaceutical Chemistry, Hebrew University, Jerusalem, 91010, Israel
SO J. Am. Chem. Soc. (**1994**), 116(16), 7319-24
CODEN: JACSAT; ISSN: 0002-7863
DT Journal
LA English
AB The nitrone 5,5-dimethyl-1-pyrroline N-oxide (DMPO) is the most common spin trap used for studying free radicals, yet its spin adducts are rapidly and irreversibly destroyed by cells. A Me substitution at the 2-position of DMPO results in the nitrone 2,5,5-trimethyl-1-pyrroline N-oxide (M3PO). Radical addn. to M3PO is expected to produce stable spin adducts; however, they have almost the same N hyperfine splitting (hfs), and, in the absence of a .beta.-hydrogen, different adducts are not distinguishable. To overcome this limitation, the synthesis of M3PO labeled with 13C at the nitronyl (C-2) or the 2-Me (.alpha. or .beta. to the aminoxyl group in the spin adduct, resp.) has been undertaken. [.alpha.-13C]M3PO was synthesized from [2-13C]acetone in a four-step pathway while [.beta.-13C]M3PO was obtained from DMPO and [13C]iodomethane. For M3PO, the nuclear magnetic moment of 13C replaces that of the .beta.-hydrogen of DMPO and provides the addnl. hfs necessary for spin adduct identification. Primary radicals, such as .bul.CH3, .bul.CO2- and .bul.OH were generated radiolytically, sonolytically, or enzymically, trapped by [13C]M3PO, and gave rise to **nitroxide** spin adducts which were identified and their magnetic parameters detd. The [13C]M3PO spin adducts were far more stable than those of DMPO. Moreover, they were less susceptible to cellular-induced destruction. However, the superoxide adduct of M3PO was unstable and did not persist.
IT **157686-92-5P 157686-93-6P 157686-94-7P**
157686-95-8P 157686-98-1P 157686-99-2P
RL: PRP (Properties); FORM (Formation, nonpreparative); PREP (Preparation)
(formation and ESR of)

L103 ANSWER 20 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:528927 HCAPLUS
DN 121:128927
TI Modification of the aerobic **cytotoxicity** of etanidazole
AU Palayoor, Sanjeewani T.; Bump, Edward A.; Malaker, Kamal; Langley, Ruth E.; Saroff, Daniel M.; Delfs, John R.; Hurwitz, Selwyn J.; Coleman, C. Norman
CS Jt. Cent. Radiat. Ther., Harvard Med. Sch., Boston, MA, USA
SO Int. J. Radiat. Oncol., Biol., Phys. (**1994**), 29(2), 289-93
CODEN: IOBPD3; ISSN: 0360-3016
DT Journal
LA English
AB To det. the feasibility of modifying the aerobic **cytotoxicity** of etanidazole without interfering with the **tumoricidal** action of radiation plus etanidazole. The aerobic **cytotoxicity** of etanidazole was studied using two different models: (1) induction of apoptosis in EL4 cells: apoptotic **DNA** fragmentation was analyzed by agarose gel electrophoresis following 24 h treatment with etanidazole alone or in combination with various modifiers; and (2) spinal cord neuronal loss in organotypic roller tube cultures: survival of acetylcholinesterase pos. ventral horn neurons was analyzed morphometrically following 72 h treatment with etanidazole alone or in combination with vitamin E succinate. Etanidazole (10 mM) induced apoptosis in EL4 cells. This effect was **suppressed** by 24 h treatment with TPA, IBMX, the free radical scavenger **TEMPOL** or vitamin E succinate. Vitamin E succinate also protected spinal cord cultures from etanidazole-induced neuronal loss. These results suggest that it might be possible to modify the neurotoxicity of etanidazole with agents that would not be expected to interfere with the

tumoricidal action of radiation plus etanidazole.
IT **2226-96-2, TEMPOL**
RL: BIOL (Biological study)
(etanidazole aerobic **cytotoxicity** modification by)

L103 ANSWER 21 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:429948 HCAPLUS
DN 121:29948
TI Pharmacokinetic properties of **nitroxide**-labeled albumin in mice
AU Liebmann, James; Bourg, John; **Krishna, Murali**; Glass, Joseph; Cook, John A.; **Mitchell, James B.**
CS Radiation Biol. Branch, Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Life Sci. (**1994**), 54(26), PL503-PL509
CODEN: LIFSAK; ISSN: 0024-3205
DT Journal
LA English
AB The authors have conjugated bovine serum albumin (BSA) with a pyrrolidinyl **nitroxide** and report on the in vivo pharmacokinetic properties of this conjugate in mice. In vivo EPR measurements of **nitroxide** were obtained after i.v. injection of 30 mg of labeled BSA by anal. of the **nitroxide** signal from the tails of mice. Following in vivo **nitroxide** measurements, the animals were sacrificed by exsanguination and organs were removed for detn. of **nitroxide** levels. The level of **nitroxide** as detd. by in vivo measurements declined exponentially with time and had a half-life (t1/2) of 7 h. Blood **nitroxide** levels also declined exponentially with time with an initial t1/2 of 70 min and a terminal t1/2 of 10 h. **Nitroxide** concn. varied among different organs; no **nitroxide** was detected within brain whereas lung had high concns. of **nitroxide**. Liver and kidney both had relatively low levels of oxidized **nitroxide**, through total **nitroxide** (reduced plus oxidized) accumulated in the kidneys with time. **Nitroxide**-labeled BSA was well tolerated by the mice, is relatively stable, and is mainly confined to the intravascular space. **Nitroxide**-labeled albumin may be useful as a contrast agent for MRI or EPR imaging.

L103 ANSWER 22 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:289592 HCAPLUS
DN 120:289592
TI Impairments in metabolism of superoxide radicals in liver tissue of **tumor**-bearing mice during development of Ehrlich ascites **carcinoma** and the normalizing effect of ruboxyl
AU Gurevich, S. M.; Vartanyan, L. S.; Nagler, L. G.
CS N. N. Semenov Inst. Chem. Phys., Moscow, Russia
SO Vopr. Med. Khim. (**1993**), 39(6), 16-20
CODEN: VMDKAM; ISSN: 0042-8809
DT Journal
LA Russian
AB Activity of the systems involved in **generation** and utilization of superoxide radicals was studied in microsomes, mitochondria, and nuclei of liver tissue from intact mice, mice with developed Ehrlich ascites **carcinoma**, and animals treated with the **antitumor** drug ruboxyl. The ratio between the rate of superoxide radicals formation and activity of superoxide dismutase (SOD) served as specific characteristic of the O2-SOD system in the corresponding compartments. During **tumor** development, the pattern studied was altered in all the subcellular organelles used, thus demonstrating impairment of free radical oxidn. status in liver tissue of **tumor**-bearing animals. Administration of ruboxyl in healthy animals led to distinct increase in O2-SOD ratio in mitochondria, while normalizing it in all cell compartments studied in **tumor**-bearing animals. Ruboxyl appears to exhibit **regulating** effect on free radical oxidn.
IT **84412-94-2**, Ruboxyl
RL: BIOL (Biological study)
(superoxide radical formation to superoxide dismutase activity ratio response to, in various cell organelles in liver)

L103 ANSWER 23 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:264641 HCAPLUS
DN 120:264641
TI Potential use of **nitroxides** in radiation **oncology**
AU Hahn, Stephen M.; **Krishna, C. Murali**; Samuni, Amram; DeGraff, William; Cuscela, Daniel O.; Johnstone, Peter; **Mitchell, James B.**
CS Radiat. Biol. Sect., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Cancer Res. (**1994**), 54(7, Suppl.), 2006s-2010s
CODEN: CNREA8; ISSN: 0008-5472
DT Journal; General Review
LA English
AB A review with 43 refs. The identification of radioprotectors is an important goal for those involved in radiation **oncol.** and for those interested in the investigation of the mechanisms of radiation **cytotoxicity**. Recently, a new class of in vitro and in vivo radioprotectors, the **nitroxides**, has been discovered. The **nitroxides** are low-mol.-wt. stable free radicals which are freely membrane permeable and which have been shown to act as superoxide dismutase mimics. Further investigation of these compds. has shown that a water-sol. **nitroxide**, **Tempol**, protects cultured Chinese hamster V79 cells from the **cytotoxicity** caused by superoxide, hydrogen peroxide, and tert-Bu hydroperoxide. **Tempol** and five other water-sol. **nitroxides** have also been shown to protect V79 cells against radiation-induced **cytotoxicity**. Potential mechanisms of protection by the **nitroxides** include oxidn. of reduced transition metals, superoxide dismutase-like activity, and scavenging of oxy- and carbon-based free radicals. In vivo studies reveal that **Tempol** protects C3H mice from the lethal effects of radiation with a dose causing 50% lethality within 30 days of 9.97 Gy and 7.84 Gy in **Tempol**-treated and saline-treated mice, resp., and a dose modification factor of 1.3. The **nitroxides** represent a new class of non-thiol radioprotectors which may also have application as general antioxidants. Addnl. work is necessary to screen other **nitroxides** for in vivo radioprotection and toxicity as well as to fully evaluate the extent to which these compds. protect **tumors**.

L103 ANSWER 24 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:211569 HCAPLUS
DN 120:211569
TI Protection from lethal irradiation by the combination of stem cell factor and **tempol**
AU Liebmann, James; **DeLuca, Anne Marie**; Epstein, Alan; Steinberg, Seth M.; Morstyn, George; **Mitchell, James B.**
CS Radiobiol. Sec., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Radiat. Res. (**1994**), 137(3), 400-4
CODEN: RAREAE; ISSN: 0033-7587
DT Journal
LA English
AB Cytokines that stimulate growth and differentiation of hematopoietic precursor cells have been used as protectors in vivo against ionizing radiation. Recently, the authors have shown that the **nitroxide** **tempol** is also an effective radiation protector in vivo. The purpose of the present study was to det. if the combination of **tempol** with stem cell factor (SCF, c-kit ligand) would provide enhanced radiation protection in C57 mice compared with the protection afforded by either agent alone. Mice were exposed to whole-body .gamma.-irradn. and assessed for survival at 30 days after irradn. No control mice survived doses of >9 Gy. Treatment of mice before and after radiation with SCF alone (100 .mu.g/kg at -20 h, -4 h and +4 h) protected mice from radiation at doses of as high as 10 Gy (76% survival). **Tempol** (350 mg/kg) given 10 min prior to radiation was a radioprotector at 9 Gy (55% survival). The combination of SCF and **tempol** increased the survival of mice exposed to radiation doses up to 11 Gy (32% survival for the combination vs 4% for SCF alone and 0% for **tempol** alone; $P < 0.001$ for the combination vs either agent

alone). Lower doses of SCF alone (1 .mu.g/kg) or **tempol** alone (275 mg/kg) did not protect mice from radiation. However, the combination of these reduced doses of SCF and **tempol** protected mice from lethal irradn. at 10 Gy. Stem cell factor and **tempol** given either singly or together were well tolerated by the animals. These data show that SCF and **tempol** are radiation protectors and that their radioprotective effects are more then additive when the agents are given together.

IT **2226-96-2, Tempol**
RL: BIOL (Biological study)
(radioprotection by stem cell factor and, of survival from .gamma.-rays)

L103 ANSWER 25 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:644760 HCAPLUS
DN 119:244760
TI The effect of oxygen at physiological levels on the detection of free radical intermediates by electron paramagnetic resonance
AU **Krishna, Murali C.**; Samuni, Amram
CS Div. Cancer Treat., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Free Radical Res. Commun. (**1993**), 18(4), 239-47
CODEN: FRRCEX; ISSN: 8755-0199
DT Journal
LA English
AB The effects of oxygen and ferricyanide on the EPR signal height of stable and persistent spin adduct **nitroxides** at commonly employed microwave powers were examd. The results show that under commonly adopted EPR spectrometer instrumental conditions, artifactual changes in the EPR signal of spin adducts occur and the best way to avoid them is by keeping the oxygen level const. using a gas-permeable cell.
IT **2226-96-2, TEMPOL 2896-70-0**, TEMPONE
RL: ANST (Analytical study)
(in detection of free radical intermediates by EPR, oxygen in relation to)

L103 ANSWER 26 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:619476 HCAPLUS
DN 119:219476
TI Spin-trapping detection of precursors of hydroxyl-radical-induced DNA damage: Identification of precursor radicals of DNA strand breaks in oligo(dC)10 and oligo(dT)10
AU Kuwabara, Mikinori; Ohshima, Hideki; Sato, Fumiaki; Ono, Akira; Matsuda, Akira
CS Fac. Vet. Med., Hokkaido Univ., Sapporo, 060, Japan
SO Biochemistry (**1993**), 32(40), 10599-606
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
AB A spin-trapping method combined with enzymic digestion and high-performance liq. chromatog. was employed to detect hydroxyl-radical-induced precursors of strand breaks in oligonucleotides ((dC)10 and (dt)10) as **DNA** models. Radicals produced as precursors of both strand breaks and base alterations were first trapped by the spin trap 2-methyl-2-nitrosopropane. The oligonucleotides contg. spin adducts were subsequently digested by snake venom phosphodiesterase to release low-mol.-wt. **nitroxide** fragments. In this way, several spin adducts were sepd. by high-performance liq. chromatog. In both oligonucleotides, ESR spectra attributable to the spin adducts derived from trapping of a precursor radical of strand breaks (the C4'-sugar radical) were obsd. To further confirm this assignment, the induction of strand breaks was examd. by polyacrylamide gel electrophoresis of 5'-32P-end-labeled oligonucleotides. Autoradiograms of the gels showed that the fragments corresponding to monomers to 9mers were formed in both oligonucleotides. When expts. were carried out under conditions in which hydroxyl radicals reacted with oligomers in the presence of the spin trap, the spin trap was found to **suppress**

the fragmentation more than it did by scavenging hydroxyl radicals, indicating that the precursor radical of strand breaks (the C4' radical) was trapped. The present expts. showed that the spin-trapping method combined with gel electrophoresis was a good approach to identify sites of radical damage which cause strand breaks in oligonucleotides (probably in **DNA**).

L103 ANSWER 27 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:551772 HCAPLUS
DN 119:151772
TI **Antitumor** activity of a new low immunosuppressive derivative of podophyllotoxin (GP-11) and its mechanisms
AU Wang, Junzhi; Tian, Xuan; Tsumura, Hideki; Shimura, Keishiro; Ito, Hitoshi
CS Sch. Med., Mie Univ., Tsu, 514, Japan
SO Anti-Cancer Drug Des. (**1993**), 8(3), 193-202
CODEN: ACDDEA; ISSN: 0266-9536
DT Journal
LA English
AB The spin-labeled deriv. of podophyllotoxin, N'-podophyllic acid-N-[3-(2,2,5,5-tetra-Me pyrrolinenyloxy)] semicarbazide (GP-11), was synthesized and tested for its **antitumor** activity against mouse transplantable **tumors**, **Sarcoma**-180, Hepatoma-A, P388 leukemia and Ehrlich ascites **carcinoma**. At an equitoxic dose, the **antitumor** activity of GP-11 was similar to that of etoposide (VP-16). However, the immunosuppressive effects of GP-11 were weaker than that of VP-16. In vitro, GP-11 and VP-16 inhibited the **proliferation** of human lymphoid leukemia Molt 4B cells and **suppressed DNA** and protein syntheses, but the effect of GP-11 and VP-16 on cell cycle progression was different. The mitotic index was increased by GP-11 and reduced by VP-16. On the basis of flow cytometry bromodeoxyuridine (BrdU)/**DNA** anal., GP-11 and VP-16 resulted in the accumulation of cells in the S and G2/M phases. G2/M arrest by GP-11 on cell cycle progression was stronger than that of VP-16, while S arrest was weaker than that of VP-16. After the removal of drugs, the arrest by GP-11 and VP-16 still existed and was irreversible. These results may provide insights into the structure-activity relationships and the design of novel derivs. of podophyllotoxin useful in **cancer** chemotherapy.
IT **68212-42-0**, 2,2,5,5-Tetramethylpyrroline-1-oxy-3-isocyanate
RL: RCT (Reactant)
(reaction of)

L103 ANSWER 28 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:486354 HCAPLUS
DN 119:86354
TI Preparation and characterization of a bifunctionally spin-labeled **mutant** of murine epidermal growth factor for saturation-transfer electron paramagnetic resonance studies of the growth factor/receptor complex
AU Rousseau, Dennis L., Jr.; Guyer, Cheryl A.; Beth, Albert H.; Papayannopoulos, Ioannis A.; Wang, Baiyang; Wu, Ray; Mroczkowski, Barbara; Staros, James V.
CS Dep. Biochem., Vanderbilt Univ., Nashville, TN, 37235, USA
SO Biochemistry (**1993**), 32(31), 7893-903
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
AB In this report the authors describe the prodn. of a [Lys3,Tyr22]-murine epidermal growth factor (mEGF) **mutant** for spin-labeling with bis(sulfo-N-succinimido)-[15N,2H16]doxyl-2-spiro-4'-pimelate ([15N,2H16]BSSDP) in order to study the rotational dynamics of the EGF/EGF receptor complex by satn.-transfer ESR (ST-EPR). Previous results indicated that the reaction of [15N,2H16]BSSDP with wild-type mEGF did not yield a product useful for ST-EPR studies of the EGF/EGF receptor complex because the major product, in which [15N,2H16]BSSDP was attached only at the amino terminus of mEGF, lacked rigid motional coupling of the spin

probe to the protein, and the more tightly coupled bidentate product was unstable. Using oligonucleotide-mediated site-directed **mutagenesis** of a synthetic gene for mEGF, the authors replaced Tyr3 with Lys and His22 with Tyr in wild-type mEGF to produce a **mutant** mEGF suitable for [15N,2H16]BSSDP labeling. The [Lys3,Tyr22]mEGF was expressed in Escherichia coli HB101 transformed with a pIN-III-ompA3-[Lys3,Tyr22]mEGF plasmid and was purified from the bacterial periplasm using a simple two step purifn. method. The [15N,2H16]BSSDP reacted with [Lys3,Tyr22]mEGF in high yield, and EPR anal. of the major product revealed tight motional coupling between the spin probe and the protein. Biol. activity, as assessed by stimulation of EGF receptor autophosphorylation and dimerization, was not affected by either the **mutations** or the addn. of the spin label. The [15N,2H16]BSSDP-modified [Lys3,Tyr22]mEGF was shown to be equipotent with mEGF in EGF receptor competition binding assays using A431 cells; in EPR studies, mEGF also was shown to specifically block [15N,2H16]BSSDP-modified [Lys3,Tyr22]mEGF binding to the EGF receptor in A431 membrane vesicles. Using the [15N,2H16]BSSDP-modified [Lys3,Tyr22]mEGF, the authors now report the first measurement of the rotational dynamics of the EGF/EGF receptor complex in A431 membrane vesicles by ST-EPR.

IT **115420-14-9**
RL: ANST (Analytical study)
(EGF **mutant** spin labeling with, for EGF-receptor interaction studies)

L103 ANSWER 29 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:73248 HCAPLUS
DN 118:73248
TI **Nitroxide**-mediated protection against x-ray- and neocarzinostatin-induced DNA damage
AU DeGraff, William G.; **Krishna, Murali C.**; Kaufman, Dwight; **Mitchell, James B.**
CS Radiat. Oncol. Branch, Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Free Radical Biol. Med. (**1992**), 13(5), 479-87
CODEN: FRBMEH; ISSN: 0891-5849
DT Journal
LA English
AB The stable free radical **Tempol** (4-hydroxy-2,2,6,6-tetramethylpiperidinyloxy) has been shown to protect against x-ray-induced **cytotoxicity** and hydrogen- or xanthine oxidase-induced **cytotoxicity** and **mutagenicity**. The ability of **Tempol** to protect against x-ray- or neocarzinostatin (NCS)-induced **mutagenicity** or DNA double-strand breaks (dsb) was studied in Chinese hamster cells. **Tempol** (50 mM) provided a protection factor of 2.7 against x-ray-induced **mutagenicity** in Chinese hamster ovary (CHO) AS52 cells, with a protection factor against **cytotoxicity** of 3.5. Using the field inversion gel electrophoresis technique of measuring DNA dsb, 50 mM **Tempol** provides a threefold redn. in DNA damage at an x-ray dose of 40 Gy. For NCS-induced damage, **Tempol** increased survival from 9% to 80% at 60 ng/mL NCS and reduced **mutation** induction by a factor of approx. 3. DNA dsb were reduced by a factor of approx. 7 at 500 ng/mL NCS. **Tempol** is representative of a class of stable **nitroxide** free radical compds. that have superoxide dismutase-mimetic activity, can oxidize metal ions such as ferrous iron that are complexed to DNA, and may also detoxify radiation-induced organoperoxide radicals by competitive scavenging. The NCS chromophore is reduced by sulfhydryls to an active form. Electron resonance (ESR) spectroscopy shows that 2-mercaptoethanol-activated NCS reacts with **Tempol** 3.5 times faster than does unactivated NCS. Thus, **Tempol** appears to inactivate the NCS chromophore before a substantial amt. of DNA damage occurs.

IT **2226-96-2, Tempol**
RL: BIOL (Biological study)
(x-ray- and neocarzinostatin-induced DNA damage prevention by)

L103 ANSWER 30 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:658165 HCAPLUS
DN 117:258165
TI **Mutagenicity** of nitroxyl compounds: structure-activity relationships
AU Gallez, B.; De Meester, C.; Debuyst, R.; Dejehet, F.; Dumont, P.
CS Dep. Pharm. Sci., Cathol. Univ. Louvain, Brussels, B-1200, Belg.
SO Toxicol. Lett. (**1992**), 63(1), 35-45
CODEN: TOLED5; ISSN: 0378-4274
DT Journal
LA English
AB Three piperidinoxyl radicals were directly **mutagenic** in Salmonella typhimurium TA 100; one pyrrolidinoxyl compd. had weaker activity, and two other pyrrolidinoxyl derivs. did not produce an increase of the spontaneous revertants. The **mutagenic** activity of the three active compds. was abolished by partial redn. with ascorbic acid, suggesting that the **mutagenicity** was linked to the free radical nature of these compds., and reduced in the presence of a cofactor supplemented rat liver subcellular fraction. The **mutagenicity** of the tested compds. was correlated to the resistance of the nitroxyl spin labels to redn.: the more reactive radicals were found to possess higher **mutagenic** activity.
IT **2154-68-9 2226-96-2 2564-83-2, Tempo 4399-80-8 14691-88-4**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**mutagenicity** of, in Ames test, structure in relation to)

L103 ANSWER 31 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:647346 HCAPLUS
DN 117:247346
TI Specificity and affinity of binding of phosphate-containing compounds to CheY protein
AU Kar, Leela; De Croos, Philomen Z.; Roman, Steven J.; Matsumura, Philip; Johnson, Michael E.
CS Dep. Med. Chem. Pharmacogn., Univ. Illinois, Chicago, IL, 60680, USA
SO Biochem. J. (**1992**), 287(2), 533-43
CODEN: BIJOAK; ISSN: 0306-3275
DT Journal
LA English
AB 1H- and 31P-NMR have been used to study the interaction of the bacterial chemotaxis protein, CheY, with ATP and a variety of other phosphates in the presence and absence of bivalent metal ions. In the metal-bound conformation, CheY will bind nucleotide phosphates and phosphates in **general**, while in the metal-free conformation CheY loses its affinity for phosphates. In the presence of low concns. of **nitroxide**-spin-labeled ATP (SL-ATP), specific proton resonances of metal-bound CheY are **suppressed**, indicating that ATP binds to a specific site on this metal-bound form of the protein. These studies also show that the same resonances are affected by the binding of SL-ATP and Mn2+, indicating that the phosphate- and metal-binding sites are close to each other and to Asp-57 (the site of phosphorylation in CheY). 1H- and 31P-NMR studies using ATP, GTP, TTP, UTP, ADP, AMP and inorg. phosphates show that the binding is not specific for adenine, and does not involve the base directly, but is mediated primarily by the phosphate groups. Expts. with a phosphorylation **mutant** (Asp-13 .fwdarw. Asn) suggest that the obsd. phosphate binding and activation of CheY by phosphorylation may be related. The results indicate that the conformational change and charge interactions brought about by the binding of a metal ion at the active site are required for CheY to interact with a phosphate. These studies also demonstrate the utility of spin-label induced relaxation in conjunction with two-dimensional-NMR measurements for exploring ligand-binding sites.

L103 ANSWER 32 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:629205 HCAPLUS
DN 117:229205

TI Identification of **nitroxide** radioprotectors
AU Hahn, Stephen M.; Wilson, Lynn; **Krishna, C. Murali**; Liebmann, James; DeGraff, William; Gamson, Janet; Samuni, Amram; Venzon, David; **Mitchell, James B.**
CS Radiobiol. Sect., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Radiat. Res. (**1992**), 132(1), 87-93
CODEN: RAREAE; ISSN: 0033-7587
DT Journal
LA English
AB The **nitroxide Tempol**, a stable free radical, has recently been shown to protect mammalian cells against several forms of oxidative stress including radiation-induced **cytotoxicity**. To extend this observation, 6 addnl. water-sol. **nitroxides** with different structural features were evaluated for potential radioprotective properties using Chinese hamster V79 cells and clonogenic assays. **Nitroxides** (10 mM) were added 10 min prior to radiation exposure and full radiation dose-response curves were detd. In addn. to **Tempol**, 5 of the 6 **nitroxides** afforded in vitro radioprotection. The best protectors were found to be the pos. charged **nitroxides**, Tempamine and 3-aminomethyl-PROXYL, with protection factors of 2.3 and 2.4, resp., compared with **Tempol**, which had a protection factor of 1.3. 3-Carboxy-PROXYL, a neg. charged **nitroxide**, provided minimal protection. DNA binding characteristics as studied by nonequil. dialysis of DNA with each of the **nitroxides** demonstrated that Tempamine and 3-amino-methyl-PROXYL bound more strongly to DNA than did **Tempol**. Since DNA is assumed to be the target of radiation-induced **cytotoxicity**, differences in protection may be explained by variabilities in affinity of the protector for the target. This study establishes **nitroxides** as a general class of new nonthiol radioprotectors and suggests other parameters that may be exploited to find even better **nitroxide** -induced radioprotection.
IT **2154-68-9 2154-70-3 2226-96-2, Tempol**
2896-70-0, 4-Oxo-**TEMPO 4399-80-8**
14691-88-4, Tempamine **54606-49-4**
RL: BIOL (Biological study)
(radioprotection by, of V79 cells survival from x-rays, DNA binding in relation to)

L103 ANSWER 33 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:587174 HCAPLUS
DN 117:187174
TI Oxoammonium cation intermediate in the **nitroxide**-catalyzed **dismutation** of superoxide
AU **Krishna, Murali C.**; Grahame, David A.; Samuni, Amram; **Mitchell, James B.**; **Russo, Angelo**
CS Div. Cancer Treatment, Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Proc. Natl. Acad. Sci. U. S. A. (**1992**), 89(12), 5537-41
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
AB The **dismutation** of superoxide (O2-) has previously been shown to be catalyzed by stable **nitroxide** compds. In the present study, the mechanism of O2- **dismutation** by various 5- and 6-membered ring **nitroxides** as superoxide dismutase mimics was studied by ESR spectrometry, UV-visible spectrophotometry, cyclic voltammetry, and bulk electrolysis. ESR signals from the carbocyclic **nitroxide** derivs. (piperidinyl, pyrrolidinyl, and pyrrolinyl) were unchanged when exposed to enzymically generated O2-, whereas, in the presence of O2- and reducing agents such as NADH and NADPH, the **nitroxides** underwent redn. to their resp. hydroxylamines. The reaction of 4-hydroxy-2,2,6,6-tetramethyl-1-hydroxypiperidine (**Tempol**-H) with O2- was measured and, in agreement with earlier reports on related compds., the rate was found to be too slow to be consistent with a mechanism of O2- **dismutation** involving the hydroxylamine as an intermediate. Voltammetric analyses of the carbocyclic **nitroxide** derivs.

revealed a reversible 1-electron redox couple at pos. potentials. In contrast, oxazolidine derivs. were irreversibly oxidized. At neg. potentials, all of the **nitroxides** studied exhibited a broad, irreversible reductive wave. The rate of O2- **dismutation** correlated with the reversible midpoint redox potential. Bulk electrolysis at pos. potentials was found to generate a **metastable** oxidized form of the **nitroxide**. The results indicated that the **dismutation** of O2- is catalyzed by the oxoammonium/ **nitroxide** redox couple for carbocyclic **nitroxide** derivs. In addn. to the 1-electron mitochondrial redn. pathway, the present results suggested the possibility that cellular bioredn. by a 2-electron pathway may occur subsequent to oxidn. of stable **nitroxides**. Furthermore, the cellular destruction of persistent spin adduct **nitroxides** may also be facilitated by a primary univalent oxidn.

IT **3637-10-3, Tempol** H
RL: RCT (Reactant)
(reaction of, with superoxide, kinetics of)

IT **2226-96-2, Tempol 2564-83-2, Tempo 2896-70-0**, Tempone **14691-88-4**, Tempamine
RL: BIOL (Biological study)
(superoxide **dismutation** by, kinetics and mechanism of, redox potential in relation to)

L103 ANSWER 34 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:503606 HCAPLUS
DN 117:103606
TI A critical evaluation of the present status of toxicity of aminoxyl radicals
AU Sosnovsky, George
CS Dep. Chem., Univ. Wisconsin, Milwaukee, WI, 53201, USA
SO J. Pharm. Sci. (**1992**), 81(6), 496-9
CODEN: JPMSAE; ISSN: 0022-3549
DT Journal
LA English
AB The literature on the toxicity of aminoxyl radicals is critically reviewed. It is concluded that, in general, the aminoxyl radicals possess a very low toxicity and are not **mutagenic**. In support of this contention, several aminoxyl radicals were evaluated in vitro. Thus, aminoxyl radicals 3-carboxy-2,2,5,5-tetramethylpyrroline-1-oxyl (I), 3-carboxy-2,2,25,5-tetramethylpyrrolidine-1-oxyl (PCA; II), 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (**Tempol**; III), and N-(1-hydroxymethyl-2,3-dihydroxypropyl)-3-carboxymamino-2,2,5,5-tetramethylpyrrolidine-1-oxyl (NAT; IV) were evaluated using Salmonella typhimurium tester strains TA 102 and TA 104, with a supplement of xanthine oxidase enzyme. I, II, and IV were found to be **nonmutagenic**, while III elicited in TA 104 only about a twofold increase in the no. of revertants above the control. This response is considered to be, at best, marginal in view of wide fluctuations of exptl. scores. The results of the present study are in agreement with those of other studies confirming the **nonmutagenicity** of aminoxyl radicals investigated to date. However, these conclusions are different from those of a study where III was tested in the presence of a generated toxic oxygen species that can cause **mutagenic** changes of the environment.

IT **2154-67-8 2154-68-9 2226-96-2 97546-74-2**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**mutagenicity** of, toxic oxygen species generation in)

L103 ANSWER 35 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:420023 HCAPLUS
DN 117:20023
TI Mechanisms of hypoxic and aerobic **cytotoxicity** of mitomycin C in Chinese hamster V79 cells
AU **Krishna, Murali C.**; DeGraff, William; Tamura, Shinji; Gonzalez, Frank J.; Samuni, Amram; **Russo, Angelo**; **Mitchell, James**

B.
CS Radiat. Oncol. Branch, Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Cancer Res. (**1991**), 51(24), 6622-8
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English
AB Mitomycin C (MMC) induced aerobic and hypoxic **cytotoxicity** in Chinese hamster V79 cells was studied to evaluate the role of the 1-electron vs. 2-electron reductive bioactivation. Superoxide dismutase, catalase, and desferal had no protective effects on the aerobic or hypoxic **cytotoxicity** of MMC, whereas **Tempol** and **Tempol**-H, which are known to interrupt and terminate radical reactions, provided partial protection under aerobic conditions. However, under hypoxic conditions, **Tempol** provided complete protection whereas **Tempol**-H was ineffective. ESR and spin-trapping investigations, designed to study the mechanisms of such protective effects, confirmed that MMC is activated by the human NADPH:cytochrome P 450 oxidoreductase to its semiquinone radical and that under aerobic conditions, the semiquinone radical reduces mol. oxygen. Under hypoxic conditions, the semiquinone of MMC reduces H2O2 to produce OH radicals as detected by ESR-spin trapping with 5,5-dimethyl-1-pyrroline N-oxide. The 1-electron reduced product of MMC was also found to reduce **Tempol** to the hydroxylamine. **Tempol**-H, whereas oxidn. of **Tempol**-H by MMC- was negligible. Cell survival studies and ESR observations indicate that the hypoxic **cytotoxicity** of MMC is mediated by 1-electron activation to its semiquinone intermediate. Under aerobic conditions, the steady state concn. of this intermediate is low due to the facile autoxidn. of the semiquinone producing O2- and H2O2 which are capable of causing oxidative **cytotoxicity**. **Tempol**, which can accept an electron from reducing radical species, completely inhibited the hypoxic **cytotoxicity** of MMC indicating MMC-, the semiquinone of MMC as the species responsible for DNA alkylation and selective hypoxic **cytotoxicity** of MMC. The results also indicate that the aerobic **cytotoxicity** is mediated by other processes in addn. to the 1-electron mediated activation.
IT **2226-96-2, Tempol 3637-10-3**
RL: BIOL (Biological study)
(mitomycin C hypoxic and aerobic **cytotoxicity** response to, bioreductive activation in relation to)

L103 ANSWER 36 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:251168 HCAPLUS
DN 116:251168
TI Topical application of **nitroxide** protects radiation-induced alopecia in guinea pigs
AU Goffman, Thomas; Cuscela, Daniel; Glass, Joseph; Hahn, Stephen; **Krishna, C. Murali**; Lupton, George; **Mitchell, James B.**
CS Radiat. Oncol. Branch, Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Int. J. Radiat. Oncol., Biol., Phys. (**1992**), 22(4), 803-6
CODEN: IOBPD3; ISSN: 0360-3016
DT Journal
LA English
AB Treatment of Chinese hamster V79 cells with stable **nitroxide** radical **TEMPOL** (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl) afforded significant protection against superoxide, hydrogen peroxide, and x-ray mediated **cytotoxicity**. Radiation-induced alopecia is a common radiotherapeutic problem. Topical application of **TEMPOL** was evaluated for possible protective effects against radiation-induced alopecia using guinea pig skin as a model. For single acute x-ray doses up to 30 Gy, **TEMPOL**, when topically applied 15 min prior to irradn. provided a marked increase in the rate and extent of new hair recovery when compared to untreated skin. **TEMPOL** was detected in treated skin specimens with ESR spectroscopy. Similar measurements of blood samples failed to show any signal resulting from topical application, nor could **TEMPOL** be detected in brain tissue after application on the scalp. **TEMPOL** represents a new class of

compds. with potential for selective cutaneous radioprotection without systemic absorption.

IT **2226-96-2, TEMPOL**
RL: BIOL (Biological study)
(radioprotection by, against alopecia from x-ray)

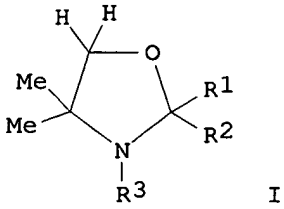
L103 ANSWER 37 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:100912 HCAPLUS
DN 116:100912
TI **Antimutagenicity** of a low molecular weight superoxide dismutase mimic against oxidative **mutagens**
AU DeGraff, William G.; **Krishna, Murali C.**; **Russo, Angelo**; **Mitchell, James B.**
CS Radiobiol. Sect., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Environ. Mol. Mutagen. (**1992**), 19(1), 21-6
CODEN: EMMUEG; ISSN: 0893-6692
DT Journal
LA English
AB A set of stable **nitroxide** free radicals that are used as spin labels have been shown to possess metal-independent superoxide dismutase-like activity. Unlike superoxide dismutase (SOD), these compds. are low mol. wt., and readily penetrate into the cell. A representative **nitroxide**, 4-hydroxy-2,2,6,6-tetramethylpiperidinyloxy (**Tempol**), was investigated for **antimutagenic** activity in the XPRT forward **mutation** assay in CHO AS52 cells. AS52 cells were exposed to hydrogen peroxide, or the hypoxanthine/xanthine oxidase superoxide generating system, in the presence or absence of 10 mM **Tempol**. **Tempol** itself was not **mutagenic** or toxic to AS52 cells. **Tempol** protected cells nearly completely from the **cytotoxic** and **mutagenic** effects of hydrogen peroxide and hypoxanthine/xanthine oxidase. It is suggested that the **antimutagenic** activity of **Tempol** is an intracellular phenomenon.
IT **2226-96-2, Tempol**
RL: BIOL (Biological study)
(active oxygen species **cytotoxicity** and **mutagenicity** in animal cell prevention by, superoxide dismutase mimic in relation to)

L103 ANSWER 38 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:577284 HCAPLUS
DN 115:177284
TI **Nitroxides** as protectors against oxidative stress
IN **Mitchell, J. B.**; Samuni, A.; DeGraff, W. G.; Hahn, S.
PA National Institutes of Health, USA
SO U. S. Pat. Appl., 38 pp. Avail. NTIS Order No. PAT-APPL-7-494 532.
CODEN: XAXXAV
DT **Patent**
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 494532	A0	19900801	US 1990-494532	19900316 <--
CA 2078287	AA	19910917	CA 1991-2078287	19910318 <--
CA 2078287	C	19961126		
WO 9113619	A1	19910919	WO 1991-US1778	19910318 <--
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
AU 9175423	A1	19911010	AU 1991-75423	19910318 <--
AU 644865	B2	19931223		
EP 520005	A1	19921230	EP 1991-906494	19910318 <--
EP 520005	B1	19970827		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 05501114	T2	19930304	JP 1991-506418	19910318 <--
EP 787492	A1	19970806	EP 1997-100145	19910318 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				

	AT 157249	E	19970915	AT 1991-906494	19910318 <--
	US 5462946	A	19951031	US 1992-859622	19920320 <--
PRAI	US 1990-494532	19900227 <--			
	EP 1991-906494	19910318 <--			
	WO 1991-US1778	19910318 <--			

OS MARPAT 115:177284
GI



I

AB Oxazole derivs. I (R1 = Me; R2 = Et, Pr, Bu, etc.; R1 with R2 = spirocyclopentane, spirocyclohexane, etc.; R3 = O, OH) and other **nitroxides**, e.g. **Tempol**, are used to protect animal tissues against oxidative stress. Thus, 2-spirocyclohexane-5,5-dimethyl-3-oxazolidinoxyl (prepn. described) protected Chinese hamster V79 cells exposed to hypoxanthine/xanthine oxidase. **Tempol** protected female C3H mice from whole body irradn.; radiation LD50 was increased approx. 25%. The compds. act as superoxide dismutase mimics.

IT **2226-96-2, Tempol**
RL: BIOL (Biological study)
(as radioprotectant and biol. antioxidant)

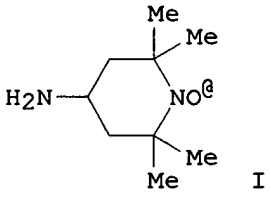
IT **55011-31-9P 67201-43-8P 128757-78-8P**
128757-79-9P 128821-74-9P 135273-94-8P
135273-95-9P 135273-96-0P 135273-97-1P
135273-98-2P 135273-99-3P 135301-17-6P
135301-18-7P 135301-19-8P 136567-25-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as superoxide dismutase mimic, for protection against oxidative stress in animal)

L103 ANSWER 39 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:488366 HCAPLUS
DN 115:88366
TI Inhibition of oxygen-dependent radiation-induced damage by the **nitroxide** superoxide dismutase mimic, **tempol**
AU **Mitchell, James B.**; DeGraff, William; Kaufman, Dwight; **Krishna, Murali C.**; Samuni, Amram; Finkelstein, Eli; Ahn, Min S.; Hahn, Stephen M.; Gamson, Janet; **Russo, Angelo**
CS Radiat. Oncol. Branch, Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Arch. Biochem. Biophys. (**1991**), 289(1), 62-70
CODEN: ABBIA4; ISSN: 0003-9861
DT Journal
LA English
AB Stable **nitroxide** radicals have been previously shown to function as superoxide dismutase (SOD) mimics and to protect mammalian cells against superoxide and H2O2-mediated oxidative stress. These unique characteristics suggested that **nitroxides**, such as 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (**Tempol**), might protect mammalian cells against ionizing radiation. Treating Chinese hamster cells under aerobic conditions with 5, 10, 50, and 100 mM **Tempol** 10 min prior to x-rays resulted in radiation protection factors of 1.25, 1.30, 2.1, and 2.5, resp. However, the reduced form of **Tempol** afforded no protection. **Tempol** treatment under hypoxic conditions did not provide radioprotection. Aerobic x-ray protection by **Tempol** could not be attributed to the induction of intracellular hypoxia, increase in intracellular glutathione, or induction

of intracellular SOD mRNA. **Tempol** thus represents a new class of non-thiol-contg. radiation protectors, which may be useful in elucidating the mechanism(s) of radiation-induced cellular damage and may have broad applications in protecting against oxidative stress.

IT **2226-96-2, Tempol**
RL: BIOL (Biological study)
(radioprotection by, of V-79 cell survival from x-rays, oxygen dependence of)

L103 ANSWER 40 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:486966 HCAPLUS
DN 115:86966
TI **Nitroxide** stable radicals protect beating cardiomyocytes against oxidative damage
AU Samuni, Amram; Winkelsberg, Dorit; Pinson, Arie; Hahn, Stephen M.; **Mitchell, James B.**; **Russo, Angelo**
CS Sch. Med., Hebrew Univ., Jerusalem, 91010, Israel
SO J. Clin. Invest. (**1991**), 87(5), 1526-30
CODEN: JCINAO; ISSN: 0021-9738
DT Journal
LA English
GI



I

AB The protective effect of stable **nitroxide** radicals (e.g., I) against oxidative damage was studied using cardiomyocyte cultures obtained from newborn rats. Monolayered cardiomyocytes were exposed to H2O2 and the effect on spontaneous beating and leakage of LDH was detd. H2O2 irreversibly blocked rhythmic beating and resulted in a significant membrane injury as shown by the release of LDH. The injury was prevented by catalase which removes H2O2 and by cell-permeable, metal-chelating agents such as desferrioxamine or bipyridine. In contrast, reagents which are excluded from the cell such as superoxide dismutase or DTPA did not protect the cells against H2O2. Five- and 6-membered ring, stable **nitroxide** radicals which have previously been shown to chem. act as low-mol.-wt., membrane-permeable, SOD-mimetic compds. provide full protection. The **nitroxides** prevented leakage of LDH and preserved normal cardiomyocyte contractility, presumably by intercepting intracellular O radicals. Alternatively, protection may result through **nitroxides** reacting with reduced transition metal ions or by detoxifying secondary org. radicals.

IT **2154-68-9**, PCA **2226-96-2, Tempol**
2564-83-2, Tempo 14691-88-4, Tempamine
16302-61-7 65162-38-1
RL: BIOL (Biological study)
(heart beat response to)

L103 ANSWER 41 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:485377 HCAPLUS
DN 115:85377
TI **Nitroxide** SOD-mimics: modes of action
AU Samuni, Amram; **Mitchell, James B.**; DeGraff, William; **Krishna, C. Murali**; Samuni, Uri; **Russo, Angelo**
CS Radiat. Oncol. Branch, Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Free Radical Res. Commun. (**1991**), 12-13(Pt. 1), 187-94
CODEN: FRRCEX; ISSN: 8755-0199

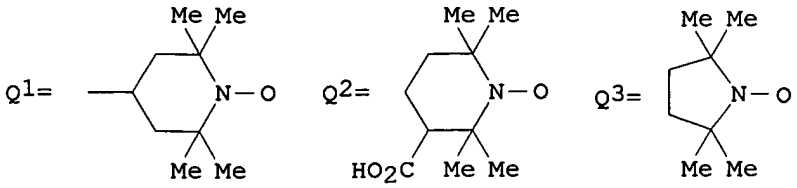
DT Journal
LA English
AB Low mol. wt. superoxide dismutase mimics have been shown to afford protection from oxidative damage. Such SOD-mimics can readily permeate cell membrane achieving sufficiently high levels both inside and outside the cell to effectively detoxify intracellular O2. Preliminary findings also indicated that metal-based and metal-free SOD-mimics can protect hypoxic cells from H2O2-induced damage. The present study explored the possibility that SOD-mimics such as desferrioxamine-Mn(III) chelate [DF-Mn] or cyclic **nitroxide** stable free radicals could protect from O2-independent damage. Killing of monolayered V79 Chinese hamster cells were induced by H2O2 or by tert-Bu hydroperoxide (t-BHP) and assayed clonogenically. Neither catalase nor native SOD protected the cells from t-BHP. In contrast, both DF-Mn and cyclic **nitroxides** protected suggesting **cytotoxic** processes independent of O2 or of O2-derived active species. The inhibition of the damage by both metal-free and metal-based SOD mimics is attributable to either SOD-mimic reacting with reduced transition metal to block the Fenton reaction and/or intercepting and detoxifying intracellular org. free radicals.
IT **2226-96-2**, 4-Hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl
RL: PRP (Properties)
(cytoprotective effect of, as superoxide dismutase mimic)

L103 ANSWER 42 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:464685 HCAPLUS
DN 115:64685
TI SOD-like activity of 5-membered ring **nitroxide** spin labels
AU Samuni, Amram; Min, Ahn; **Krishna, C. Murali; Mitchell, James B.; Russo, Angelo**
CS Div. Cancer Treat., NCI, Bethesda, MD, 20892, USA
SO Adv. Exp. Med. Biol. (**1990**), 264(Antioxid. Ther. Prev. Med.), 85-92
CODEN: AEMBAP; ISSN: 0065-2598
DT Journal
LA English
AB The hydroxylamine, 2-ethyl-1-hydroxy-2,5,5-trimethyl-3-oxazolidinoxyl (OXANO), has superoxide dismutase (SOD)-like activity and protects mammalian cells against oxidative damage. The radical-radical reaction between stable **nitroxide** and O2-.bul. is not limited to OXANO but is shared by other **nitroxides** which exhibit, therefore, SOD-like activity. Despite differences in charge, size, nd lipophilicity the **nitroxides** studied readily react with O2-.bul..
IT **2226-96-2 2564-83-2 3229-73-0 4399-80-8 14691-88-4 134998-33-7 134998-34-8**
RL: BIOL (Biological study)
(superoxide dismutase-like activity of, structure in relation to)

L103 ANSWER 43 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:157185 HCAPLUS
DN 114:157185
TI Nitrosourea derivatives showing **antitumor** and **mutagenic** activity
IN Emanuel, N. M.; Sen, V. D.; Golubev, V. A.; Bogdanov, G. N.; Vasil'eva, L. S.; Konovalova, N. P.
PA Institute of Chemical Physics, Chernogolovka, USSR
SO U.S.S.R.
From: Otkrytiya, Izobret. 1990, (23), 260.
CODEN: URXXAF
DT **Patent**
LA Russian
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI SU 1259650	A1	19900623	SU 1984-3850244	19841227 <--

GI



AB The title derivs. R1(CH2)nNR3C(O)N(NO)R3 (R1 = Q1, Q2, Q3; R2 = H, Me; R3 = Me, (CH2)2Cl; n = 0-2) are provided; 6 specific derivs. are disclosed.

IT **83144-39-2 97241-83-3 97579-81-2 132414-34-7 132414-35-8 132414-36-9**
RL: BIOL (Biological study)
(**neoplasm** inhibitor and **mutagen**)

L103 ANSWER 44 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:57081 HCAPLUS
DN 114:57081
TI **Nitroxides** block DNA scission and protect cells from oxidative damage
AU Samuni, Amram; Godinger, Dina; Aronovitch, Jacob; **Russo, Angelo; Mitchell, James B.**
CS Sch. Med., Hebrew Univ., Jerusalem, 91010, Israel
SO Biochemistry (**1991**), 30(2), 555-61
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
AB The protective effect of cyclic stable **nitroxide** free radicals, having SOD-like activity, against oxidative damage was studied by using Escherichia coli xthA DNA repair-deficient **mutant** hypersensitive to H2O2. Oxidative damage induced by H2O2 was assayed by monitoring cell survival. The metal chelator 1,10-phenanthroline (OP), which readily interchelates into DNA, potentiated the H2O2-induced damage. The extent of in vivo DNA scission and degrdn. was studied and compared with the loss of cell viability. The extent of DNA breakage correlated with cell killing, supporting previous suggestions that DNA is the crucial cellular target of H2O2 **cytotoxicity**. The xthA cells were protected by catalase but not by superoxide dismutase (SOD). Both five- and six-membered ring **nitroxides**, having SOD-like activity, protected growing and resting cells from H2O2 toxicity, without lowering H2O2 concn. To check whether **nitroxides** protect against O2.bul.--independent injury also, the expts. were repeated under hypoxia. These **nitroxides** also protected hypoxic cells against H2O2, suggesting alternative modes of protection. Since **nitroxides** were found to reoxidize DNA-bound iron(II), the present results suggest that **nitroxides** protect by oxidizing reduced transitional metals, thus interfering with the Fenton reaction.
IT **2226-96-2, Tempol 2564-83-2, Tempo 14691-88-4 16302-61-7 65162-38-1**, OXANO
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(hydrogen peroxide toxicity to Escherichia coli response to)

L103 ANSWER 45 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1990:494214 HCAPLUS
DN 113:94214
TI Superoxide reaction with **nitroxides**
AU Samuni, Amram; **Krishna, C. Murali; Mitchell, James B.**; Collins, Christi R.; **Russo, Angelo**
CS Div. Cancer Treat., NCI, Bethesda, MD, 20892, USA
SO Free Radical Res. Commun. (**1990**), 9(3-6), 241-9
CODEN: FRRCEX; ISSN: 8755-0199

DT Journal
LA English
AB Stable, free radical **nitroxides** are commonly used ESR spectroscopy tools. However, it has recently been found that ESR observable signal from 5-membered ring spin-adducts or stable label **nitroxides** is lost or diminished by reaction with superoxide. A similar radical-radical annihilation was not found for six-membered ring **nitroxide** radicals. To discern why six-membered ring **nitroxides** are not reduced under superoxide flux generated by hypoxanthine/xanthine oxidase, spectrophotometric (Cyt CIII) and chemiluminescence (lucigenin) and ESR assays were used to follow the reactions. Spectrophotometry and chemiluminescence clearly demonstrated that the six-membered piperidine-1-oxyl compds. (**TEMPO**, TEM-POL, and TEMPAMIN) rapidly react with superoxide: rate consts. at pH 7.8 ranging from 7 .times. 104 to 1.2 .times. 105M-1 s-1. The absence of detectable ESR signal loss results from facile re-oxidn. of the corresponding hydroxylamine by superoxide. To fully corroborate the efficiency of the 6-membered **nitroxide** superoxide dismutase activity, they were shown to protect fully mammalian cells from oxidative damage resulting from exposure to the superoxide and hydrogen peroxide generating system hypoxanthine/xanthine oxidase. Since six-membered cyclic **nitroxides** react with superoxide about 2 orders of magnitude faster than the corresponding 5-membered ring **nitroxides**, they may ultimately be more useful as superoxide dismutase mimetic agents.
IT **2226-96-2, TEMPOL 2564-83-2, TEMPO 14691-88-4**
RL: ANST (Analytical study)
(superoxide reaction with)

L103 ANSWER 46 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1990:135122 HCAPLUS
DN 112:135122
TI Biologically active metal-independent superoxide dismutase mimics
AU **Mitchell, James B.**; Samuni, Amram; **Krishna, Murali C.**; DeGraff, William G.; Ahn, Min S.; Samuni, Uri; **Russo, Angelo**
CS Div. Cancer Treat., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Biochemistry (**1990**), 29(11), 2802-7
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
AB Attempts to increase intracellular concns. of superoxide dismutase (SOD) by direct application are complicated because SOD, being a relatively large mol., does not readily cross cell membranes. Here, a set of stable **nitroxides** was identified that possess SOD-like activity, have the advantage of being low-mol.-wt. membrane-permeable, and metal-independent, and at pH 7.0 have reaction rate consts. with superoxide in the range of 1.1 .times. 103-1.3 .times. 106 M-1 s-1. These SOD mimics protect mammalian cells from damage induced by hypoxanthine/xanthine oxidase and H2O2, although they exhibit no catalase-like activity. In addn., the **nitroxide** SOD mimics rapidly oxidize DNA-Fe (II) and thus may interrupt the Fenton reaction and prevent formation of deleterious OH radicals and/or higher oxidn. states of metal ions. Whether by SOD-like activity and/or interception of an electron from redox-active metal ions they protect cells from oxidative stress and may have use in basic and applied biol. studies.
IT **16263-51-7 16302-61-7 63035-93-8 65162-38-1**, Oxano **125569-48-4**
RL: RCT (Reactant)
(superoxide **dismutation** by, as superoxide dismutase mimic)

L103 ANSWER 47 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1989:3623 HCAPLUS
DN 110:3623
TI **Nitroxide** spin label. A novel metal-free low molecular weight superoxide dismutase mimic

AU Samuni, Amrum; **Krishna, C. Murali**; Riesz, Peter; Finkelstein, Eli; **Russo, Angelo**
CS Div. Cancer Treat., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO J. Biol. Chem. (**1988**), 263(34), 17921-4
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB 2-Ethyl-1-hydroxy-2,5,5-trimethyl-3-oxazolidine (OXANOH), the 1-electron redn. product of the stable **nitroxide** radical, 2-ethyl-2,5,5-trimethyl-3-oxazolidinoxyl (OXANO), is reported oxidized by O2-, and its oxidn. has been proposed as a method for assaying O2-. O2- can both reduce OXANO and oxidize OXANOH. The resp. rate consts., k1 and k2, were detd. using 2 O2--generating systems (xanthine oxidase/xanthine and ionizing radiation). OXANOH oxidn. and OXANO redn. are both inhibitable by superoxide dismutase, pH-dependent (4.5-9.3), and result in a steady state distribution of [OXANO] and [OXANOH], independent of their initial concns., i.e. the OXANO/OXANOH couple exhibits a metal-independent superoxide dismutase-like function. Thus it provides a prototype for future development of improved low-mol.-wt. superoxide dismutase mimics which will also function in cellular hydrophobic (aprotic) compartments such as membranes.
IT **65162-38-1 67201-43-8**
RL: BIOL (Biological study)
(as superoxide dismutase model)

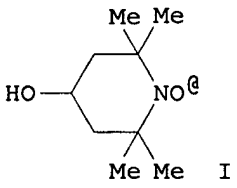
L103 ANSWER 48 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1988:563475 HCAPLUS
DN 109:163475
TI Pyrroxamide, a nonionic nitroxyl spin label contrast agent for magnetic resonance imaging. **Mutagenesis** and cell survival
AU Gordon, Deborah G.; Brasch, Robert C.; Ogan, Marc D.; Deen, Dennis
CS Brain Tumor Res. Cent., Univ. California, San Francisco, CA, USA
SO Invest. Radiol. (**1988**), 23(8), 616-20
CODEN: INVRAV; ISSN: 0020-9996
DT Journal
LA English
AB Pyrroxamide is a newly tested nonionic monomeric nitroxyl compd. with demonstrated effectiveness for magnetic resonance imaging contrast enhancement at doses .gtoreq.10-3M. Pyrroxamide and its hydroxylamine metabolic deriv. were tested in concns. from 10-9 to 10-2M with a battery of **cytotoxic** and **mutagenic** assays using mammalian Chinese hamster ovary cells. Loci-specific **mutation** induction was examd. at the hypoxanthine-guanine phosphoribosyltransferase and the Na+/K+-ATPase loci, both in the presence and absence of a liver microsomal metabolic activating mixt. (S-9 mix). Cell survival and induction of sister chromatid exchanges also were studied. All tests yielded neg. results indicating that pyrroxamide and its hydroxylamine deriv. were both noncytotoxic and **nonmutagenic** at the doses tested.
IT **97546-74-2 113788-70-8**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**cytotoxicity** and **mutagenicity** of)

L103 ANSWER 49 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1987:133483 HCAPLUS
DN 106:133483
TI Nucleophilic targets in **carcinogenesis, mutagenesis** and chemotherapy of **cancer**
AU Raikov, Z.; Christova-Georgieva, N.; Raikova, E.
CS Lab. Mol. Oncol., Stara Zagora, 6000, Bulg.
SO Med. Hypotheses (**1987**), 22(1), 15-22
CODEN: MEHYDY; ISSN: 0306-9877
DT Journal
LA English
AB An hypothesis is suggested, which emphasizes the role in **carcinogenesis** of the attack on low mol. nucleophilic substances (LMN) by electrophilic agents - chem. **carcinogens**, phys.

factors, and **antitumor** alkylating agents. The significance of the degree of nucleophilicity (electronic charge, order of bonds, and index of valence) as a locus minoris resistentiae of the LMN in the electrophilic attack on the latter is emphasized as well as the probable role of the hydrogenated pteridines in influencing **carcinogenesis** by means of ascorbate, tocopherol, SH-contg. compds., etc.

IT **95596-73-9**, R50
RL: RCT (Reactant)
(reaction of, with folic acid and tetrahydrolic acid)

L103 ANSWER 50 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1987:14473 HCAPLUS
DN 106:14473
TI **Mutagenicity** of **nitroxide** free radicals
AU Sies, Helmut; Mehlhorn, Rolf
CS Dep. Biochem., Univ. California, Berkeley, CA, USA
SO Arch. Biochem. Biophys. (**1986**), 251(1), 393-6
CODEN: ABBIA4; ISSN: 0003-9861
DT Journal
LA English
GI



I

AB Stable **nitroxides tempol** (I) [**2226-96-2**] or PCAOL [**2154-67-8**] increased **mutation** rates in Salmonella typhimurium strain TA 104 (strain sensitive to oxidative damage) more than in strain TA 4124 (strain contg. the oxyR1 **mutant** allele for the defense against oxidative stress; it produces, e.g., high concns. of catalase and superoxide dismutase). The **mutation** rate in strain TA 104 increased by I plus superoxide (generated by xanthine oxidase and hypoxanthine) more than by I alone; strain TA 4124 **mutation** rate was not affected by the addn. of superoxide-generating systems. Mechanism of the **nitroxides mutagenicity** is suggested contg. sulfenyl hydroperoxides or subsequent oxidn. products as the active **mutagenic** species. This could be a model for the **carcinogenicity** of arom. amines.

IT **2154-67-8**, PCAOL **2226-96-2**, **Tempol**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**mutagenicity** of, in Staphylococcus aureus, superoxide effect on, mechanism of)

L103 ANSWER 51 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1986:545894 HCAPLUS
DN 105:145894
TI Interaction of a spin-labeled phenylalanine analog with normal and sickle hemoglobins: detection of site-specific interactions through spin-label-induced proton NMR relaxation
AU Lee, Yu Hwei; Currie, Bruce L.; Johnson, Michael E.
CS Dep. Med. Chem. Pharmacogn., Univ. Illinois, Chicago, IL, 60680, USA
SO Biochemistry (**1986**), 25(19), 5647-54
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
AB It was previously shown that N-[(2,2,5,5-tetramethyl-1-oxypyrrolidin-3-

yl)carbonyl]-L-phenylalanine tert-bityl ester (SL-Phe) [**92455-23-7**] exhibits specific binding to Hb A [9034-51-9] and an antiaggregation activity more than 2 orders of magnitude greater than that of phenylalanine. Transverse HNMR relaxation measurements have been used to investigate the interaction of SL-Phe with Hb mols. by use of the resonances assigned to the C2 protons of the .beta.2 His, the .beta.143 His, and the .beta.146 or .beta.97 His residues as intrinsic probes. Distance calcns. using the paramagnetically induced relaxation data suggest that the SL-Phe binding site is .apprx.12-16 .ANG. away from the C2 protons of the .beta.2 His and the .beta.146 or .beta.97 His residues in the (carbonmonoxy)Hb tetramer; the deoxyHb, the distances are .apprx.14-17 .ANG. between the SL-Phe binding site and the C2 protons of the .beta.2 His, the .beta.143 His, and the .beta.146 His residues. Calcns. using the (carbonmonoxy)Hb crystal at. coordinates only restrict the probable SL-Phe binding region to the full F and H helices of the .beta.-chain and a small section of the .alpha.-chain. For deoxyHb, the distance calcns. provide greater restrictions on the probable binding region, limiting it to small sections of the .beta.-chain F, G, and H helices near the EF bend and to a few residues on the .alpha.-chain. The coincidence between the probable binding regions for both (carbonmonoxy)Hb and deoxyHb suggests that the binding site is probably the same for both Hb forms. Most of the residues whose coordinates are consistent with the distance calcns. for deoxygenated Hb are at or near the lateral contact site that is complementary to the .beta.6 **mutation** site within the sickle Hb [9035-22-7] double-strand structure that is considered to be the fundamental unit of the sickle Hb polymer fiber. Binding of SL-Phe at this region could thus explain its strong inhibitory activity. Further work in defining the binding stereochem. should be helpful in developing antisickling agents with higher activity and specificity.

IT **92455-23-7**
RL: BIOL (Biological study)
(HbA and HbS binding sites for, of humans)

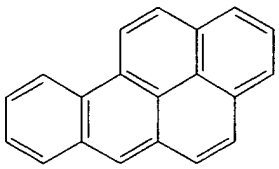
L103 ANSWER 52 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1984:145 HCAPLUS
DN 100:145
TI Irreversible binding of quinacrine to nucleic acids during horseradish peroxidase- and prostaglandin synthetase-catalyzed oxidation
AU Sinha, Birandra Kumar
CS Lab. Environ. Biophys., Natl. Inst. Environ. Health Sci., Research Triangle Park, NC, 27709, USA
SO Biochem. Pharmacol. (**1983**), 32(17), 2604-7
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English
AB Quinacrine [83-89-6] produced **nitroxide** radicals during horseradish peroxidase [9003-99-0]- and prostaglandin synthetase [9055-65-6]-catalyzed oxidn. The intermediate(s) formed during enzymic oxidn. bound irreversibly to nucleic acids. Significantly more drug was bound to denatured DNA than to native DNA. These findings are discussed in light of **mutagenic** properties of antibacterial and **antitumor** acridines.

L103 ANSWER 53 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1983:483509 HCAPLUS
DN 99:83509
TI Structure activity studies with N-nitrosamines using Salmonella typhimurium and Escherichia coli
AU Rao, T. K.; Epler, J. L.; Lijinsky, W.
CS Biol. Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830, USA
SO IARC Sci. Publ. (**1982**), 41(N-Nitroso Compd: Occurrence Biol. Eff.), 543-51
CODEN: IARCCD; ISSN: 0300-5038
DT Journal
LA English
AB The **mutagenic** activities of a large no. of nitrosamines were

detd. using S. typhimurium histidine reversion and E. coli arginine reversion assays. The E. coli assay not only substantiated the Salmonella results, but also identified certain **carcinogens** (N-nitrosopyrroline [10552-94-0], 3,4-dibromonitrosopyrrolidine [69112-97-6], and N-nitrosomethylethylamine [10595-95-6]) as **mutagens**, although they were missed in the Salmonella assay. The cyclic nitrosamines exhibited a close correlation between their **mutagenic** and **carcinogenic** properties, while no such relation was evident with the aliph. nitrosamines. Substitution with alkyl or hydroxy groups did not affect the biol. activity (**mutagenic/carcinogenic**) of cyclic nitrosamines. However, when positions alpha to the N-nitroso groups were substituted with Me groups, the biol. activity was eliminated. Substitution with halogens enhanced whereas carboxyl substitution eliminated the biol. activity.

IT **6130-93-4**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**carcinogenicity** and **mutagenicity** of)

L103 ANSWER 54 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1982:212262 HCAPLUS
DN 96:212262
TI Screening of antioxidants and other compounds for **antimutagenic** properties towards benzo[a]pyrene-induced **mutagenicity** in strain TA98 of Salmonella typhimurium
AU Calle, Luz M.; Sullivan, Paul D.
CS Dep. Chem., Ohio Univ., Athens, OH, 45701, USA
SO Mutat. Res. (**1982**), 101(2), 99-114
CODEN: MUREAV; ISSN: 0027-5107
DT Journal
LA English
GI



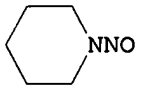
I

AB Among compds. which are known to inhibit **carcinogenicity**, retinol [68-26-8], phenothiazine [92-84-2], disulfiram [97-77-8], phenethylisothiocyanate [2257-09-2] and phenylisothiocyanate [103-72-0] were the most effective inhibitors of benzo[a]pyrene (BP)(I) [50-32-8] **mutagenicity** in S. typhimurium strain TA98, being effective at equimolar concns. Several other compds. showed inhibition at higher concns. of antioxidant and the remainder showed little or no inhibition. Dose-response curves were obtained for the 17 most active compds. No general pattern of inhibition is obvious from these studies, inhibitors are not drawn from any single class of compds., nor does a particular compd. necessarily appear to inhibit >1 **mutagen**.

IT **2226-96-2**
RL: BIOL (Biological study)
(benzopyrene **mutagenicity** in relation to)

L103 ANSWER 55 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1978:59209 HCAPLUS
DN 88:59209
TI **Mutagenicity** of N-nitrosopiperidines with Salmonella typhimurium/microsomal activation system
AU Rao, T. K.; Hardigree, A. A.; Young, J. A.; Lijinsky, W.; Epler, J. L.
CS Biol. Div., Oak Ridge Natl. Lab., Oak Ridge, Tenn., USA
SO Mutat. Res. (**1977**), 56(2), 131-45

CODEN: MUREAV
DT Journal
LA English
GI



I

AB Using S. typhimurium tester strains, N-nitropiperidine (I) [100-75-4] and various substituted nitrosopiperidines were examd. for their **mutagenic** potency. Most of the nitrosopiperidines require metabolic activation. Phenobarbital appears to be the most effective inducer of the rat liver enzymes. A correlation between **mutagenicity** and **carcinogenic** potency of these compds. was also obsd. The C atoms .alpha. to the N-nitroso group seem important since blockage of those positions reduces or eliminates **mutagenicity** as well as **carcinogenicity** of the nitrosopiperidine.
IT **640-01-7 6130-93-4 55556-90-6**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**mutagenicity** of, **carcinogenicity** in relation to)

L103 ANSWER 56 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1972:471730 HCAPLUS
DN 77:71730
TI N-Acetoxy-N-acetylaminoarenes and nitrosoarenes. One-electron nonenzymic and enzymic oxidation products of various **carcinogenic** aromatic acethydroxamic acids
AU Bartsch, Helmut; Miller, James A.; Miller, Elizabeth C.
CS Med. Cent., Univ. Wisconsin, Madison, Wis., USA
SO Biochim. Biophys. Acta (**1972**), 273(1), 40-51
CODEN: BBACAQ
DT Journal
LA English
AB A no. of **carcinogenic** aromatic acetohydroxamic acids (e.g. N-hydroxy-N-acetyl derivs. of 2-aminofluorene, 3-aminofluorene, 4-aminostilbene, 1-aminonaphthalene, 2-aminonaphthalene, 2-aminophenanthrene, and 4-aminobiphenyl) are readily oxidized by alk. Fe(CN)63- or Ag2O. The free **nitroxide** radicals thus formed **dismutate** in org. soln. according to 2nd-order kinetics to yield the corresponding N-acetoxy-N-acetylaminoarenes and nitrosoarenes. The structures of the latter products were established by mass and ir spectrum analyses. Evidence was obtained for a similar 1-electron oxidn. of these acetohydroxamic acids with horseradish peroxidase and H2O2 at pH 7. One-electron oxidn. of N-hydroxy-2-acetylaminofluorene was also demonstrated with lactoperoxidase and human myeloperoxidase. The possible relevance of a similar peroxidative attack in vivo to the **carcinogenic** activities of some aromatic amines and amides is discussed.

L103 ANSWER 57 OF 57 HCAPLUS COPYRIGHT 2000 ACS
AN 1971:496675 HCAPLUS
DN 75:96675
TI Metabolic activation of the **carcinogen** N-hydroxy-N-2-acetylaminofluorene. III. Oxidation with horseradish peroxidase to yield 2-nitrosofluorene and N-acetoxy N-2-acetylaminofluorene
AU Bartsch, Helmut; Hecker, Erich
CS Biochem. Inst., Ger. Cancer Res. Cent., Heidelberg, Ger.
SO Biochim. Biophys. Acta (**1971**), 237(3), 567-78
CODEN: BBACAQ
DT Journal
LA English

GI For diagram(s), see printed CA Issue.
AB The **carcinogen** N-hydroxy-2-acetylaminofluorene (I) is converted by 1-electron oxidants to a free **nitroxide** radical which **dismutates** to N-acetoxy-2-acetylaminofluorene (II) and 2-nitrosofluorene (III). In the present study, the same oxidn. was achieved with horseradish peroxidase and hydrogen peroxide. The free radical intermediate was detected by its ESR signal, and the yields of II and III were detd. under a no. of conditions. The addn. of transfer RNA to the reaction mixt. contg. tritiated II gave tRNA-bound radioactivity. The addn. of guanosine gave a reaction product which seemed to be N-(guanosin-8-yl)-2-acetylaminofluorene. Attempts to demonstrate the formation of a **nitroxide** free radical or its **dismutation** products with rat liver mixed function oxidase systems failed.

=> fil medline

FILE 'MEDLINE' ENTERED AT 11:40:04 ON 28 OCT 2000

FILE LAST UPDATED: 27 OCT 2000 (20001027/UP). FILE COVERS 1960 TO DATE.

MEDLINE has been reloaded to reflect the annual MeSH changes made by the National Library of Medicine for 2000. Enter HELP RLOAD for details.

The OLDMEDLINE file segment now contains data from 1958 through 1965. Enter HELP CONTENT for details.

Left, right, and simultaneous left and right truncation are available in the Basic Index. See HELP SFIELDS for details.

THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE SUBSTANCE IDENTIFICATION.

=> d his l105-

(FILE 'REGISTRY' ENTERED AT 11:16:32 ON 28 OCT 2000)

FILE 'REGISTRY' ENTERED AT 11:17:06 ON 28 OCT 2000

FILE 'HCAPLUS' ENTERED AT 11:18:00 ON 28 OCT 2000

FILE 'MEDLINE' ENTERED AT 11:18:54 ON 28 OCT 2000

```
L105        200 S L1 OR L2
L106       2198 S L4
L107       1663 S NITROGEN OXIDES/CT,CN
L108       2407 S CYCLIC N-OXIDES/CT,CN
L109       5814 S L105-L108
L110       1386 S NITROXIDE
L111       6577 S L109,L110
                E GENES, REGULAT/CT
L112       5708 S L111 AND PY<=1997
L113          0 S L112 AND P53
L114        288 S L112 AND (C4. OR TUMOR CELLS, CULTURED+NT)/CT
L115          2 S (GENES, SUPPRESSOR, TUMOR+NT OR GENES, REGULATOR+NT)/CT AND L
L116         55 S (GENE EXPRESSION+NT OR GENE EXPRESSION REGULATION+NT)/CT AND
L117         55 S L115,L116
L118          5 S L114 AND L117
L119          0 S L105 AND L118
L120          0 S L110 AND L118
L121          7 S L110 AND L117
L122          5 S L105 AND L117
L123        144 S TEMPOL
L124        200 S 2226-96-2
L125        249 S L123,L124
L126        171 S L125 AND PY<=1997
```

```
L127         20 S L126 AND L114-L117
                E MITCHELL J/AU
L128        747 S E3,E5
                E RUSSO A/AU
L129        872 S E2-E16
                E CHERUKURI /AU
L130          1 S E6
                E KRISHNA /AU
L131         36 S E3,E21
L132          2 S E49
L133         88 S E58-E59
                E DELUCA A/AU
L134         55 S E3,E7
                E DE LUCA A/AU
L135        258 S E3,E4
L136         59 S L111 AND L128-L135
L137         32 S L125 AND L128-L135
L138         59 S L136,L137
L139         47 S L138 AND PY<=1997
L140          4 S L139 AND C4./CT
L141          4 S L127 AND L138
L142         22 S L127,L140,L141
L143         41 S L139 NOT L142
L144          7 S L143 AND (RADIATION-PROTECTIVE AGENTS OR CHROMOSOMES+NT OR CH
L145         11 S L143 AND SUPEROXIDE DISMUTASE/CT,CN
L146         40 S L142,L144,L145
L147         35 S L138 NOT L146
L148         75 S L146,L147
L149          5 S L148 NOT AB/FA
L150         70 S L148 NOT L149
L151         58 S L150 AND PY<=1997

     FILE 'MEDLINE' ENTERED AT 11:40:04 ON 28 OCT 2000

=> d all tot


L151 ANSWER 1 OF 58  MEDLINE
AN   1998074225     MEDLINE
DN   98074225
TI   Managing the excited skin syndrome: patch testing hyperirritable skin.
AU   Mitchell J; Maibach H I
CS   University California Medical School, San Francisco 94143, USA.
SO   CONTACT DERMATITIS, (1997 Nov) 37 (5) 193-9.  Ref: 59
     Journal code: DP7. ISSN: 0105-1873.
CY   Denmark
DT   Journal; Article; (JOURNAL ARTICLE)
     General Review; (REVIEW)
     (REVIEW, TUTORIAL)
LA   English
FS   Priority Journals
EM   199804
EW   19980401
AB   Inflammation-modulating phenomena (IMPs), humoral and cellular, fluctuate
     during the course of irritant and allergic contact dermatitis influencing
     irritability of the skin. The patch test procedure is a biological assay,
     a titration of responses of IMPs which can produce hyporeactivity or
     hyperirritability of the skin of patients who have dermatitis (PDs) and a
     single patch test is a 'snapshot' of the tempo of an evolving
     process. The excited skin syndrome (ESS) refers to hyperirritability from
     clinical and patch test dermatitis creating false-positive patch test
     reactions which are not reproducible when dermatitis and IMPs have
     subsided. During ESS, the threshold for irritancy decreases and irritant
     reactions increase. Patch test concentrations should be determined and ESS
     investigated in PDs having enhanced IMPs, not in 'normal' individuals, and
     if a patch test result is important to a patient the test should be
```

performed more than once. Variable reproducibility is inherent in the patch test method, but ESS can be managed by appropriate testing and retesting, and search for relevance.

CT Check Tags: Case Report; Female; Human; Male
Adult
*Dermatitis, Allergic Contact: DI, diagnosis
Dermatitis, Allergic Contact: IM, immunology
False Positive Reactions
*Hypersensitivity, Delayed: IM, immunology
Middle Age
*Patch Tests: AE, adverse effects
Patch Tests: MT, methods
Reproducibility of Results
Sensitivity and Specificity

L151 ANSWER 2 OF 58 MEDLINE
AN 1998062483 MEDLINE
DN 98062483
TI Detection and analyses of ascorbyl radical in cerebrospinal fluid and serum of acute lymphoblastic leukemia.
AU Nakagawa K; Kanno H; Miura Y
CS Radio Isotope Research Center, Department of Pediatrics, Fukushima Medical College, 1 Hikarigaoka, Fukushima-shi, 960-12, Japan.. nakagawa@cc.fmu.ac.jp
SO ANALYTICAL BIOCHEMISTRY, **(1997 Dec 1)** 254 (1) 31-5.
Journal code: 4NK. ISSN: 0003-2697.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199803
EW 19980305
AB We have detected and analyzed a free radical in human cerebrospinal fluid (CSF) of acute lymphoblastic leukemia (ALL) for the first time using electron paramagnetic resonance (EPR) at ambient temperature. We have also introduced an alternative capillary method to measure the radical. EPR spectra of the radical show a characteristic doublet with hyperfine coupling value of 1.8 G and g = 2.005. Based on EPR measurements, computer simulation, and literature values, we have determined that the species is ascorbyl radical (AsR). The radical has been investigated in CSF samples from ALL patients having no therapy, undergoing chemotherapy, and following therapy. Determination of the ascorbyl radical concentrations in CSF and serum was attempted using known concentrations of a nitroxyl radical. In addition, comparison in CSF and serum for ALL has been made along with statistical analyses of the data obtained. We found that AsR in CSF and serum has a strong correlation in patients undergoing chemotherapy ($n = 57$, $r = 0.57$, $P < 0.0001$). Ascorbate in CSF and serum show good correlation in patients having therapy but not for patients after therapy.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Antineoplastic Agents: TU, therapeutic use
*Ascorbic Acid: AN, analysis
Ascorbic Acid: BL, blood
Ascorbic Acid: CF, cerebrospinal fluid
Colorimetry: MT, methods
Cyclic N-Oxides
Electron Spin Resonance Spectroscopy
Free Radicals: AN, analysis
Leukemia, Lymphocytic, Acute: BL, blood
Leukemia, Lymphocytic, Acute: CF, cerebrospinal fluid
Leukemia, Lymphocytic, Acute: DT, drug therapy
***Leukemia, Lymphocytic, Acute: ME, metabolism**
Regression Analysis
Spin Labels
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 50-81-7 (Ascorbic Acid)

CN 0 (Antineoplastic Agents); **0 (Cyclic N-Oxides)**; 0 (Free Radicals); 0 (Spin Labels)

L151 ANSWER 3 OF 58 MEDLINE
AN 1998025416 MEDLINE
DN 98025416
TI **Tempol** inhibits neutrophil and hydrogen peroxide-mediated DNA damage.
AU Hahn S M; **Mitchell J B**; Shacter E
CS Radiation Biology Branch, National Cancer Institute, Bethesda, MD 20892, USA.
SO FREE RADICAL BIOLOGY AND MEDICINE, **(1997)** 23 (6) 879-84.
Journal code: FRE. ISSN: 0891-5849.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
EW 19980104
AB Inflammatory conditions characterized by neutrophil activation are associated with a variety of chronic diseases. Reactive oxygen species are produced by activated neutrophils and produce DNA damage which may lead to tissue damage. Previous studies have shown that activated murine neutrophils induce DNA strand breaks in a target plasmacytoma cell, RIMPC 2394. We studied the effect of a water soluble **nitroxide** anti-oxidant, **Tempol**, on murine neutrophil induction of DNA strand breaks in this system. Murine neutrophils were isolated from the peritoneal cavity of BALB/cAn mice after an i.p. injection of pristane oil. Neutrophils were activated by the phorbol ester PMA and co-incubated with RIMPC 2394 cells. Control alkaline elution studies revealed progressive DNA strand breaks in RIMPC cells with time. The addition of **Tempol** to the incubation mixture prevented DNA damage in a dose dependent fashion. Five mM **Tempol** provided complete protection. **Tempol** protection against DNA strand breaks was similar for both stimulated neutrophils and exogenously added hydrogen peroxide. Measurement of hydrogen peroxide produced by stimulated neutrophils demonstrated that **Tempol** did not decrease hydrogen peroxide concentration. Oxidation of reduced metals, thereby interfering with the production of hydroxyl radical, is the most likely mechanism of **nitroxide** protection, although superoxide dismutase (SOD) like activity and scavenging of carbon-based free radicals may also account for a portion of the observed protection. The anti-oxidant activity of **Tempol** inhibited DNA damage by activated neutrophils. The **nitroxides** as a class of compounds may have a role in the investigation and modification of inflammatory conditions.
CT Check Tags: Animal
*Antioxidants: PD, pharmacology
Cells, Cultured
***Cyclic N-Oxides: PD, pharmacology**
*DNA Damage: DE, drug effects
*Hydrogen Peroxide: TO, toxicity
Mice
Mice, Inbred BALB C
Neutrophil Activation: DE, drug effects
*Neutrophils: DE, drug effects
Neutrophils: ME, metabolism
Peritoneal Cavity: CY, cytology
Plasmacytoma
Reactive Oxygen Species: ME, metabolism
Respiratory Burst: DE, drug effects
Tumor Cells, Cultured
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 7722-84-1 (Hydrogen Peroxide)
CN 0 (Antioxidants); **0 (Cyclic N-Oxides)**; 0 (Reactive Oxygen Species)

L151 ANSWER 4 OF 58 MEDLINE
AN 97252526 MEDLINE
DN 97252526
TI Evaluation of **tempol** radioprotection in a murine tumor model.
AU Hahn S M; Sullivan F J; **DeLuca A M; Krishna C M;** Wersto N; Venzon D; **Russo A; Mitchell J B**
CS Radiation Biology Branch, National Cancer Institute, Bethesda, MD 20892, USA.
SO FREE RADICAL BIOLOGY AND MEDICINE, **(1997)** 22 (7) 1211-6.
Journal code: FRE. ISSN: 0891-5849.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199710
EW 19971001
AB **Tempol**, a stable **nitroxide** free radical compound, is an in vitro and in vivo radioprotector. Previous studies have shown that **Tempol** protects C3H mice against whole-body radiation-induced bone marrow failure. In this study, the radioprotection of tumor tissue was evaluated. RIF-1 tumor cells were implanted in female C3H mice 10 d prior to radiation. Groups of mice were injected intraperitoneally with **Tempol** (275 mg/kg) or PBS followed 10 min later by a single dose of radiation to the tumor bed. Tumor growth curves generated after 10 and 33.3 Gy doses of radiation showed no difference in growth between the **Tempol**- and PBS-treated animals. A full radiation dose-response experiment revealed a tumor control dose in 50% of the animals in 30 d (TCD(50/30)) value of 36.7 Gy for **Tempol**-treated mice and 41.8 Gy for saline-treated mice suggesting no protection of the RIF-1 tumor by **Tempol**. Tumor pharmacokinetics were done to determine why **Tempol** differentially protected bone marrow and not tumor cells. Differential reduction of **Tempol** in the RIF-1 tumor and bone marrow was evaluated with EPR spectroscopy 10, 20, and 30 min after injection. Bioreduction of **Tempol** to its corresponding hydroxylamine (which is not a radioprotector) occurred to a greater extent in RIF-1 tumor cells compared to bone marrow. We conclude that the differences in radioprotection may result from enhanced intratumor bioreduction of **Tempol** to its nonradioprotective hydroxylamine analogue. The **nitroxides** as a class of compounds may provide a means to exploit the redox differences between normal tissues and tumors.
CT Check Tags: Animal; Female
Bone Marrow: DE, drug effects
Bone Marrow: RE, radiation effects
Cell Division: DE, drug effects
Cyclic N-Oxides: ME, metabolism
***Cyclic N-Oxides: PD, pharmacology**
Cyclic N-Oxides: PK, pharmacokinetics
Electron Spin Resonance Spectroscopy
Mice
Mice, Inbred C3H
Neoplasm Transplantation
Neoplasms, Experimental: ME, metabolism
***Neoplasms, Experimental: PA, pathology**
Neoplasms, Experimental: RT, radiotherapy
*Radiation Tolerance: DE, drug effects
*Radiation-Protective Agents: PD, pharmacology
Radiation-Protective Agents: PK, pharmacokinetics
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**
CN **0 (Cyclic N-Oxides)**; 0 (Radiation-Protective Agents)

L151 ANSWER 5 OF 58 MEDLINE
AN 97165397 MEDLINE
DN 97165397
TI Direct evidence for in vivo **nitroxide** free radical production from a new antiarrhythmic drug by EPR spectroscopy.
AU Twomey P; Taira J; DeGraff W; **Mitchell J B; Russo A;**

Krishna M C; Hankovszky O H; Frank L; Hideg K
CS Radiation Biology Branch, National Cancer Institute, NIH, Bethesda, MD 20892, USA.
SO FREE RADICAL BIOLOGY AND MEDICINE, **(1997)** 22 (5) 909-16.
Journal code: FRE. ISSN: 0891-5849.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199706
AB The new Class I anti-arrhythmic agent 2,2,5,5-tetramethyl-3-pyrroline-1-carboxamide derivative, is currently being evaluated in clinical trials in patients with a high risk for cardiac arrhythmias. In this study we show that this antiarrhythmic drug can be chemically converted to the **nitroxide** free radical analog. Further, using an in vivo Electron Paramagnetic Resonance (EPR) spectroscopy model by detecting free radicals in the distal portion of the tail of an anesthetized mouse, we demonstrate that the drug is oxidized to the corresponding **nitroxide**. In vitro studies using Chinese hamster V79 cells suggest that the oxidation products of the drug, namely, the hydroxylamine and the **nitroxide** protect against oxidative damage induced by hydrogen peroxide (H2O2). Taken together, our results suggest that, in addition to the antiarrhythmic effects of the parent drug, sufficient levels of **nitroxides** may accumulate from the parent drug in vivo to provide antioxidant defense to cardiac tissue that may be subject to ischemia and oxidation-driven injury.
CT Check Tags: Animal; Female; Human; Support, Non-U.S. Gov't
Anti-Arrhythmia Agents: CH, chemistry
Anti-Arrhythmia Agents: ME, metabolism
*Anti-Arrhythmia Agents: PD, pharmacology
Antioxidants: CH, chemistry
Antioxidants: ME, metabolism
Antioxidants: PD, pharmacology
Arrhythmia: DT, drug therapy
Arrhythmia: ME, metabolism
Cell Line
Electron Spin Resonance Spectroscopy
Free Radicals: ME, metabolism
Hamsters
Hemeproteins: ME, metabolism
Mice
Mice, Inbred C3H
Myocardial Reperfusion Injury: DT, drug therapy
Myocardial Reperfusion Injury: ME, metabolism
***Nitrogen Oxides: ME, metabolism**
Oxidation-Reduction
RN 14332-28-6 (nitroxyl)
CN 0 (Anti-Arrhythmia Agents); 0 (Antioxidants); 0 (Free Radicals); 0 (Hemeproteins); **0 (Nitrogen Oxides)**

L151 ANSWER 6 OF 58 MEDLINE
AN 97149761 MEDLINE
DN 97149761
TI Modulatory effect of **tempol** on toxicity and antitumor activity of 6-mercaptopurine and on P450 cytochrome level.
AU Konovalova N P; Diatchkovskaya R F; Volkova L M; Varfolomeev V N
CS Institute of Chemical Physics, Russian Academy of Sciences, Chernogolovka, Moscow Region, Russia.
SO NEOPLASMA, **(1996)** 43 (5) 341-6.
Journal code: NVO. ISSN: 0028-2685.
CY Czech Republic
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199704
EW 19970402

AB Low selectivity of contemporary antitumor drugs requires a search for its improvement. In this context, nitroxyl radicals are of interest as promising pharmacological agents. The introduction of nitroxyl radical into the structure of antitumor cytostatics was found to reduce considerably their general and specific toxicity. In this work, we demonstrate a detoxifying effect of **tempol** upon its combined injection with cytostatics at their absolute lethal dose in the intact mice as well as an improvement of sensitivity of tumor-bearing animals to 6-MP. **Tempol** is shown to normalize the level of oxidized form of P450 cytochrome in a liver, reduced as a result of the injection of 6-MP.
CT Check Tags: Animal; Female
*Antimetabolites, Antineoplastic: PD, pharmacology
***Cyclic N-Oxides: PD, pharmacology**
*Cytochrome P-450: DE, drug effects
Cytochrome P-450: ME, metabolism
Drug Synergism
*Liver: DE, drug effects
Liver: EN, enzymology
***Mammary Neoplasms, Experimental: DT, drug therapy**
***Mammary Neoplasms, Experimental: EN, enzymology**
Mice
Mice, Inbred C57BL
*6-Mercaptopurine: PD, pharmacology
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 50-44-2 (6-Mercaptopurine); 9035-51-2 (Cytochrome P-450)
CN 0 (Antimetabolites, Antineoplastic); **0 (Cyclic N-Oxides)**

L151 ANSWER 7 OF 58 MEDLINE
AN 96421594 MEDLINE
DN 96421594
TI Do **nitroxide** antioxidants act as scavengers of O2-. or as SOD mimics?.
AU **Krishna M C; Russo A; Mitchell J B;** Goldstein S; Dafni H; Samuni A
CS Molecular Biology, Jerusalem, 91120, Israel.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, **(1996 Oct 18)** 271 (42) 26026-31.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199701
EW 19970104
AB Stable **nitroxide** radicals were reported to act as SOD mimics and catalyze the dismutation of O2-. through two different catalytic pathways including reductive and oxidative reaction mechanisms (Samuni, A., Krishna, C. M., Riesz, P., Finkelstein, E. & Russo, A. (1988) J. Biol Chem. 263, 17921-17924). Recent studies directly monitoring O2-. and employing kinetics analysis did not reveal SOD activity of **nitroxides** (Weiss, R. H., Flickinger, A. G., Rivers, W. J., Hardy, M. M., Aston, K. W., Ryan, U. S. & Riley, D. P. (1993) J. Biol. Chem. 268, 23049-23054). Such discrepancy may result in cases where distinction of stoichiometric scavengers from catalytic detoxifiers of O2-. is not readily feasible. **Nitroxides** are effective antioxidants that protect against oxidative injury in various pathological processes. The distinction of their SOD mimic activity from O2-. scavenging was established by examining the validity of direct and indirect methods employed to assay SOD-like catalytic activity. Kinetics analysis along with direct EPR monitoring were used to study the mechanism underlying **nitroxide** reactions with O2-.. The **nitroxide** EPR signal decayed in the presence of NADH but otherwise did not decrease with time, thus substantiating its catalytic role in O2-. dismutation. The catalytic rate constants for O2-., dismutation, determined for the **nitroxides** tested, were found to increase with [H+], indicating that .OOH rather than O2-. is oxidizing the **nitroxide**. The

results demonstrate the limitations associated with direct kinetics analysis in evaluating SOD mimic activity, underscoring the need for independent assays for valid discrimination of SOD mimics from stoichiometric scavengers of O2-..
CT Check Tags: Support, Non-U.S. Gov't
*Antioxidants: ME, metabolism
Binding, Competitive
Cyclic N-Oxides: ME, metabolism
Cytochrome c: ME, metabolism
Electron Spin Resonance Spectroscopy
*Free Radical Scavengers: ME, metabolism
Free Radicals: ME, metabolism
Hydrogen-Ion Concentration
Kinetics
Molecular Mimicry
***Nitrogen Oxides: ME, metabolism**
NAD: ME, metabolism
*Oxygen: ME, metabolism
***Superoxide Dismutase: ME, metabolism**
Superoxides: ME, metabolism
RN 11062-77-4 (Superoxides); 14332-28-6 (nitroxyl); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 53-84-9 (NAD); 7782-44-7 (Oxygen); 9007-43-6 (Cytochrome c)
CN **EC 1.15.1.1 (Superoxide Dismutase)**; 0 (Antioxidants); **0 (Cyclic N-Oxides)**; 0 (Free Radical Scavengers); 0 (Free Radicals); **0 (Nitrogen Oxides)**

L151 ANSWER 8 OF 58 MEDLINE
AN 96421593 MEDLINE
DN 96421593
TI Stimulation by **nitroxides** of catalase-like activity of hemeproteins. Kinetics and mechanism.
AU **Krishna M C**; Samuni A; Taira J; Goldstein S; **Mitchell J B**; **Russo A**
CS Radiation Biology Branch, NCI, National Institutes of Health, Bethesda, Maryland 20892, USA.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, **(1996 Oct 18)** 271 (42) 26018-25.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199701
EW 19970104
AB The ability of stable **nitroxide** radicals to detoxify hypervalent heme proteins such as ferrylmyoglobin (MbFeIV) produced in the reaction of metmyoglobin (MbFeIII) and H2O2 was evaluated by monitoring O2 evolution, H2O2 depletion, and redox changes of the heme prosthetic group. The rate of H2O2 depletion and O2 evolution catalyzed by MbFeIII was enhanced by stable **nitroxides** such as 4-OH-2,2,6,6-tetramethyl-piperidinoxyl (TPL) in a catalytic fashion. The reduction of MbFeIV to MbFeIII was the rate-limiting step. Excess TPL over MbFeIII enhanced catalase-like activity more than 4-fold. During dismutation of H2O2, [TPL] and [MbFeIV] remained constant. NADH caused: (a) inhibition of H2O2 decay; (b) progressive reduction of TPL to its respective hydroxylamine TPL-H; and (c) arrest/inhibition of oxygen evolution or elicit consumption of O2. Following depletion of NADH the evolution of O2 resumed, and the initial concentration of TPL was restored. Kinetic analysis showed that two distinct forms of MbFeIV might be involved in the process. In summary, by shuttling between two oxidation states, namely **nitroxide** and oxoammonium cation, stable **nitroxides** enhance the catalase mimic activity of MbFeIII, thus facilitating H2O2 dismutation accompanied by O2 evolution and providing protection against hypervalent heme proteins.
CT Check Tags: Animal; Support, Non-U.S. Gov't
Antioxidants: ME, metabolism

*Catalase: ME, metabolism
Cell Line
Cricetulus
Cyclic N-Oxides: ME, metabolism
Electron Spin Resonance Spectroscopy
Free Radicals: ME, metabolism
Hamsters
Hydrogen Peroxide: ME, metabolism
Kinetics
Models, Chemical
Molybdenum: ME, metabolism
Molybdoferredoxin: ME, metabolism
*Myoglobin: ME, metabolism
***Nitrogen Oxides: ME, metabolism**
NAD: ME, metabolism
Oxidation-Reduction
Oxygen: ME, metabolism
RN 14332-28-6 (nitroxyl); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 53-84-9 (NAD); 7439-98-7 (Molybdenum); 7722-84-1 (Hydrogen Peroxide); 7782-44-7 (Oxygen)
CN EC 1.11.1.6 (Catalase); 0 (Antioxidants); **0 (Cyclic N-Oxides)**; 0 (Free Radicals); 0 (Molybdoferredoxin); 0 (Myoglobin); **0 (Nitrogen Oxides)**

L151 ANSWER 9 OF 58 MEDLINE
AN 96374533 MEDLINE
DN 96374533
TI [Nitroxyl radical **Tempol** as a modulator of toxic and antineoplastic effect of 6-mercaptopurine].
Nitroksil'nyi radikal **tempol** kak moduliator toksicheskogo i protivoopukholevogo deistviia 6-merkaptopurina.
AU Konovalova N P; D'iachkovskaia R F; Volkova L M; Varfolomeev V N
SO VOPROSY ONKOLOGII, **(1996)** 42 (3) 57-63.
Journal code: XJU. ISSN: 0507-3758.
CY RUSSIA: Russian Federation
DT Journal; Article; (JOURNAL ARTICLE)
LA Russian
FS Priority Journals; Cancer Journals
EM 199612
AB Both intact mice and those with transplantable adenocarcinoma 755 were used in the investigation. The nitroxyl radical **Tempol** was shown to cut down the toxicity of 6-mercaptopurine and potentiate its antitumor effect to a certain degree. The study results suggest on the basis of an investigation of cytochrome P450 and some other evidence that said effect of **Tempol** might be due, at least, in part to antioxidant activity.
CT Check Tags: Animal; Male
***Adenocarcinoma: DT, drug therapy**
*Antimetabolites, Antineoplastic: TO, toxicity
*Antimetabolites, Antineoplastic: TU, therapeutic use
*Antineoplastic Agents: AI, antagonists & inhibitors
Antineoplastic Agents: TO, toxicity
*Antioxidants: PD, pharmacology
***Cyclic N-Oxides: PD, pharmacology**
Dose-Response Relationship, Drug
Drug Administration Schedule
Drug Synergism
English Abstract
Mice
Mice, Inbred C57BL
Survival Analysis
*6-Mercaptopurine: AI, antagonists & inhibitors
6-Mercaptopurine: TO, toxicity
*6-Mercaptopurine: TU, therapeutic use
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 50-44-2 (6-Mercaptopurine)

CN 0 (Antimetabolites, Antineoplastic); 0 (Antineoplastic Agents); 0 (Antioxidants); **0 (Cyclic N-Oxides)**

L151 ANSWER 10 OF 58 MEDLINE
AN 96240320 MEDLINE
DN 96240320
TI Electron paramagnetic resonance imaging of rat heart with **nitroxide** and polynitroxyl-albumin.
AU Kuppusamy P; Wang P; Zweier J L; **Krishna M C; Mitchell J B**; Ma L; Trimble C E; Hsia C J
CS Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland 21224, USA.
NC HL-17655 (NHLBI)
HL-38324 (NHLBI)
HL-53860 (NHLBI)
SO BIOCHEMISTRY, **(1996 Jun 4)** 35 (22) 7051-7.
Journal code: A0G. ISSN: 0006-2960.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199610
AB Electron paramagnetic resonance (EPR) imaging utilizing stable nitroxyl radicals is a promising technique for measuring free radical distribution, metabolism, and tissue oxygenation in organs and tissues [Kuppusamy, P., Chzhan, M., Vij, K., Shteynbuk, M., Lefer, D. J., Giannella, E., & Zweier, J. L. (1994) Proc. Natl. Acad. Sci. U.S.A. 91, 3388-3392]. However, the technique has been limited by the rapid reduction of **nitroxide** in vivo to its hydroxylamine derivative, a diamagnetic, EPR-inactive species. In this report a novel, polynitroxylated derivative of human serum albumin is shown to be capable of reoxidizing the hydroxylamine back to **nitroxide** in vivo. Polynitroxyl-albumin (PNA) is shown to be effective in maintaining the signal intensity of the **nitroxide** 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (**TEMPOL** or TPL) in the ischemic isolated rat heart, allowing the acquisition of high-resolution three-dimensional (3D) EPR images of the heart throughout a prolonged 2.5 h period of global cardiac ischemia. In serial transverse sections of the 3D image, TPL intensity maps of the heart showed cardiac structure with submillimeter resolution. TPL intensities in coronary arteries and myocardium showed that **nitroxide** concentration decreases with increasing distance from large blood vessels. These results demonstrate that EPR imaging in vivo is possible using **nitroxides** in conjunction with PNA. In addition to its utility in the emerging technology of EPR imaging, the greatly prolonged half-life of TPL observed in the presence of PNA may facilitate the therapeutic application of **nitroxides** in a variety of disease processes.
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Coronary Vessels: ME, metabolism
***Cyclic N-Oxides: ME, metabolism**
*Electron Spin Resonance Spectroscopy: MT, methods
Free Radicals: ME, metabolism
Hydroxylamines: ME, metabolism
Kinetics
*Myocardial Ischemia: ME, metabolism
*Myocardium: ME, metabolism
Nitrogen Oxides: ME, metabolism
Oxidation-Reduction
Permeability
Rats
Serum Albumin: ME, metabolism
Spin Labels
RN 14332-28-6 (nitroxyl); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 7803-49-8 (Hydroxylamine)
CN **0 (Cyclic N-Oxides)**; 0 (Free Radicals); 0 (Hydroxylamines); **0 (Nitrogen Oxides)**; 0 (Serum Albumin); 0 (Spin Labels)

L151 ANSWER 11 OF 58 MEDLINE
AN 96200316 MEDLINE
DN 96200316
TI Adjunctive treatment of murine neuroblastoma with 6-hydroxydopamine and **Tempol**.
AU Purpura P; Westman L; Will P; Eidelman A; Kagan V E; Osipov A N; Schor N F
CS Department of Pediatrics, University of Pittsburgh, Pennsylvania 15213, USA.
NC CA47161 (NCI)
SO CANCER RESEARCH, **(1996 May 15)** 56 (10) 2336-42.
Journal code: CNF. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199608
AB Currently available therapy for disseminated neuroblastoma affords only a 5-20% 5-year survival rate. We have attempted to design targeted chemotherapy for this disease by exploiting the dopamine uptake system on neuroblastoma cells. 6-Hydroxydopamine (6OHDA) is a neurotransmitter analogue, which generates cytolytic oxygen radicals in neuroblastoma cells that take it up. It is, however, predictably, systemically toxic, because of its spontaneous oxidation. Its toxicity is particularly severe in the sympathetic nervous system, because this tissue selectively concentrates dopamine and its analogues. Lowering the dose of 6OHDA below toxic levels prohibitively compromises its antitumor effect. To avoid both the systemic and sympathetic nervous system toxicity yet retain the antitumor efficacy of 6OHDA, we have used the antioxidant **Tempol** adjunctively with 6OHDA. Administration of **Tempol** (250 mg/kg, i.p.) 10 min prior to administration of toxic doses of 6OHDA (350 or 400 mg/kg, i.p.) resulted in a decrease in the mortality rate, sympathetic nervous system impairment, and activity impairment compared with those seen with 6OHDA alone. Tumor weights from mice administered saline or **Tempol** alone were 3.6 +/- 1.9 and 2.9 +/- 0.7 g, respectively. In contrast, mice administered **Tempol** followed by 6OHDA had an average tumor weight of 0.7 +/- 0.3 g. Tumor incidence was also reduced from 80-100% to 40%. Studies performed using electron spin resonance spectroscopy suggest that **Tempol** acts in this system by reacting directly with both the 6OHDA radical and, in the presence of iron, its oxidation product, the hydroxyl radical.
CT Check Tags: Animal; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*Adrenergic Agents: TU, therapeutic use
*Antioxidants: TU, therapeutic use
Blepharoptosis: CI, chemically induced
Catalase: PD, pharmacology
***Cyclic N-Oxides: TU, therapeutic use**
*Dopamine: ME, metabolism
Drug Screening Assays, Antitumor
Electron Spin Resonance Spectroscopy
*Free Radical Scavengers: TU, therapeutic use
Iron: ME, metabolism
Mice
Mice, Inbred A
Neoplasm Transplantation
***Neuroblastoma: DT, drug therapy**
***Neuroblastoma: ME, metabolism**
*Neuroprotective Agents: TU, therapeutic use
Oxidopamine: TO, toxicity
*Oxidopamine: TU, therapeutic use
Peroxidase: PD, pharmacology
*Reactive Oxygen Species: ME, metabolism
Single-Blind Method
Spin Labels
Sympathetic Nervous System: DE, drug effects

RN 1199-18-4 (Oxidopamine); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 51-61-6 (Dopamine); 7439-89-6 (Iron)
CN EC 1.11.1.6 (Catalase); EC 1.11.1.7 (Peroxidase); 0 (Adrenergic Agents); 0 (Antioxidants); **0 (Cyclic N-Oxides)**; 0 (Free Radical Scavengers); 0 (Neuroprotective Agents); 0 (Reactive Oxygen Species); 0 (Spin Labels)

L151 ANSWER 12 OF 58 MEDLINE
AN 96140768 MEDLINE
DN 96140768
TI Modulation of sensitivity to mitomycin C and a dithiol analogue by **tempol** in non-small-cell lung cancer cell lines under hypoxia.
AU Bando T; Kasahara K; Shibata K; Numata Y; Heki U; Shirasaki H; Iwasa K; Fujimura M; Matsuda T
CS Third Department of Internal Medicine, Kanazawa University School of Medicine, Japan.
SO JOURNAL OF CANCER RESEARCH AND CLINICAL ONCOLOGY, **(1996)** 122 (1) 21-6.
Journal code: HL5. ISSN: 0171-5216.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199604
AB We examined the mechanisms involved in the bioactivation of mitomycin C (MMC) and a newly developed MMC analogue: 7-N-(2-([2-(gamma-L-glutamylamino)ethyl]dithio)ethyl)mitomycin C, KW-2149, in non-small-cell lung cancer (NSCLC) cell lines under aerobic and hypoxic conditions. To investigate these mechanisms, we used MMC-resistant non-small-cell lung cancer cell lines (PC-9/MC4) that had been established in our laboratory from the parent PC-9 cell line by continuous exposure to MMC. We previously reported that the MMC-resistant cell line (PC-9/MC4) was poor in NAD(P)H dehydrogenase (quinone) activity and approximately 6-fold more resistant than the parent cells (PC-9) to MMC on 2-h exposure under aerobic conditions. In this study, the subline PC-9/MC4 was 6.7-fold more resistant to MMC than PC-9, the parent cell line, under aerobic conditions, and 5.2-fold more resistant under hypoxic conditions after 2-h exposure to MMC. However, on co-incubation with **tempol**, an inhibitor of the one-electron reduction pathway, the sensitivity of PC-9/MC4 to MMC was impaired under hypoxic conditions, but the impairment was not evident under aerobic conditions. KW-2149, the newly developed MMC analogue, was cytotoxic for both PC-9/MC4 and PC-9 cells, and the sensitivity of both cell lines to KW-2149 was not changed by exposure to hypoxic conditions or by coincubation with **tempol**. There were no significant differences in the intracellular uptake of MMC and the activities of cytosolic detoxification enzymes between the PC-9 and PC-9/MC4 cell lines. These results support the hypothesis that the one-electron reduction pathway plays a partial role in the bioactivation of MMC, but not of KW-2149, and that KW-2149 is excellent at circumventing resistance to MMC in NSCLC.
CT Check Tags: Human
*Antineoplastic Agents: PD, pharmacology
*Antioxidants: PD, pharmacology
Biotransformation
***Carcinoma, Non-Small-Cell Lung: DT, drug therapy**
Carcinoma, Non-Small-Cell Lung: ME, metabolism
Carcinoma, Non-Small-Cell Lung: PA, pathology
Cell Division: DE, drug effects
Cell Hypoxia
***Cyclic N-Oxides: PD, pharmacology**
Cytochrome Reductases: ME, metabolism
Drug Combinations
Drug Resistance, Neoplasm
***Lung Neoplasms: DT, drug therapy**
Lung Neoplasms: ME, metabolism
Lung Neoplasms: PA, pathology

*Mitomycin: AA, analogs & derivatives
*Mitomycin: PD, pharmacology
NAD(P)H Dehydrogenase (Quinone): ME, metabolism
Tumor Cells, Cultured: DE, drug effects
RN 118359-59-4 (KW 2149); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 50-07-7 (Mitomycin)
CN EC 1.6.2. (Cytochrome Reductases); EC 1.6.2.2 (cytochrome b(5) reductase); EC 1.6.99.2 (NAD(P)H Dehydrogenase (Quinone)); 0 (Antineoplastic Agents); 0 (Antioxidants); **0 (Cyclic N-Oxides)**; 0 (Drug Combinations)

L151 ANSWER 13 OF 58 MEDLINE
AN 95391709 MEDLINE
DN 95391709
TI Pronounced activation of protein kinase C, ornithine decarboxylase and c-jun proto-oncogene by paraquat-generated active oxygen species in WI-38 human lung cells.
AU Kuo M L; Lee K C; Lin J K; Huang T S
CS Institute of Toxicology, college of Medicine National Taiwan University, Taipei, Republic of China.
SO BIOCHIMICA ET BIOPHYSICA ACTA, **(1995 Aug 31)** 1268 (2) 229-36.
Journal code: A0W. ISSN: 0006-3002.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199512
AB Paraquat (methyl viologen, PQ) is a widely used herbicide that produces oxygen-derived free radicals and severely injures human lungs. In this study we examined the effects of PQ on the protein kinase C (PKC), ornithine decarboxylase (ODC) and c-jun oncogene expression in WI-38 human lung cells. Exposure of cells to 25-200 microM PQ resulted in an increase of [3H]phorbol dibutyrate (PDBu) binding and PKC redistribution in a dose-dependent manner. Interestingly, a superoxide dismutase mimic, 4-hydroxyl-2,2,6,6-tetramethyl-piperidine-1-oxyl (**Tempol**, 2.5 mM) and catalase (400 micrograms/ml) could significantly reduce the PQ-stimulated increase of phorbol ester binding and particular PKC phosphorylating activity, but dimethylsulfoxide (DMSO, 1.5%), an effective .OH trapping agent, failed to prevent this stimulation. In addition, an endogenous substrate of PKC, 80 kDa protein, was found to be highly phosphorylated in intact WI-38 cells treated with 50 microM PQ. The increase of phosphorylated proteins could be completely or partly abolished by **Tempol** or catalase, but only the phosphorylation of 80 kDa protein was diminished by protein kinase C inhibitor, 1-(5-isoquinolinyl-sulfonyl)-2-methylpiperazine (H-7). A maximal peak of ODC activity was observed at 6 h of treatment with 50 microM PQ. PQ induced activity was reduced at the following rates, **Tempol** 85%, DMSO 80% and catalase 45%, but H-7 failed to do so. Furthermore, we found that the level of c-jun mRNA was transiently increased by PQ and the peak appeared at 1 h of treatment. When correlated with the PKC result, **Tempol**, catalase and H-7 all effectively blocked PQ-elicited c-jun transcript expression, but DMSO only exhibited a weakly inhibitory effect. We therefore propose that superoxide anion (O2- and H2O2 generated by PQ could activate PKC and lead to induction of c-jun gene expression; on the other hand, O2- and .OH might trigger other kinase pathways to elevate ODC activity. Finally, the sequential expression of c-jun oncogene and ODC may cooperate to relieve the oxidative damages elicited by PQ.
CT Check Tags: Human; Support, Non-U.S. Gov't
Cell Line
Enzyme Activation
Gene Expression: DE, drug effects
*Genes, jun
Kinetics
*Lung: DE, drug effects
Lung: ME, metabolism
*Ornithine Decarboxylase: ME, metabolism
*Paraquat: TO, toxicity

*Protein Kinase C: ME, metabolism
*Reactive Oxygen Species: ME, metabolism
RN 4685-14-7 (Paraquat)
CN EC 2.7.1.- (Protein Kinase C); EC 4.1.1.17 (Ornithine Decarboxylase); 0 (Reactive Oxygen Species)

L151 ANSWER 14 OF 58 MEDLINE
AN 95376591 MEDLINE
DN 95376591
TI Neurophysiological consequences of **nitroxide** antioxidants.
AU Hahn S M; Lepinski D L; **DeLuca A M; Mitchell J B;** Pellmar T C
CS Radiation Biology Branch, National Cancer Institute, Bethesda, MD 20892, USA..
SO CANADIAN JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY, **(1995 Mar)** 73 (3) 399-403.
Journal code: CJM. ISSN: 0008-4212.
CY Canada
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199512
AB **Nitroxides** are antioxidant compounds that have been shown to provide radioprotection in vivo and in vitro. Radioprotection in vivo is limited by toxicity, which appears to be neurologic in nature. To further evaluate the toxicity of these compounds, three representative **nitroxides, Tempol**, Tempamine, and **Tempo**, were examined in slices of guinea pig hippocampus. Each **nitroxide** increased the population spike and caused potentiation of excitatory postsynaptic potential--spike coupling. Repetitive activity and epileptiform activity were observed at the highest concentrations of **Tempo** and Tempamine. **Tempol** was the least toxic compound in this system, followed by Tempamine and **Tempo**. Additional studies are necessary to further define the effects of **nitroxides** on the central nervous system and to develop strategies to mitigate these effects.
CT Check Tags: Animal; In Vitro; Male
*Antioxidants: PD, pharmacology
Cyclic N-Oxides: PD, pharmacology
Electrophysiology
Epilepsy: CI, chemically induced
Epilepsy: PP, physiopathology
Evoked Potentials: DE, drug effects
Guinea Pigs
*Hippocampus: CY, cytology
Hippocampus: DE, drug effects
Microelectrodes
***Nitrogen Oxides: AI, antagonists & inhibitors**
Spin Labels
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl); 2564-83-2 (TEMPO)**
CN 0 (Antioxidants); **0 (Cyclic N-Oxides); 0 (Nitrogen Oxides)**; 0 (Spin Labels)

L151 ANSWER 15 OF 58 MEDLINE
AN 95339547 MEDLINE
DN 95339547
TI Effects of antioxidants on fiber mutagenesis.
AU Hei T K; He Z Y; Suzuki K
CS Center for Radiological Research, College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA..
NC ES 05801 (NIEHS)
ES 05786 (NIEHS)
SO CARCINOGENESIS, **(1995 Jul)** 16 (7) 1573-8.
Journal code: C9T. ISSN: 0143-3334.
CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199510
AB Recent studies from this laboratory have shown that asbestos fibers are mutagenic in cultured mammalian cells when assayed using a system that can detect multilocus deletions. Southern analysis of the induced mutants shows that the majority contain large deletions ranging in size from a few thousand to several million basepairs. In the present study, the effects of free radical scavenging enzymes on the cytotoxic and mutagenic potential of chrysotile fibers were examined using the human-hamster hybrid (AL) cells. Exponentially growing cells were treated with graded doses of fibers for a 24 h period either in the presence or absence of catalase, superoxide dismutase (SOD) or **Tempol**. Fiber-exposed cells were treated with the various enzymes either concurrently with the fiber or extended through the entire expression period. While the survival of AL cells treated with graded doses of chrysotile fibers with or without a concurrent treatment with SOD and catalase was not significantly different, the mutation yield at the S1 locus was significantly reduced in cells treated with these antioxidant enzymes. Furthermore, cells treated with the enzymes for a prolonged period were not better protected than those treated only during fiber treatment. The SOD mimic **nitroxide , Tempol**, had no effect on either the survival or mutagenic yield of chrysotile fibers. While SOD and catalase reduced the mutagenic potency of asbestos fibers in AL cells, they did not alter the molecular spectrum of fiber-induced mutagenesis. Our results indicate that antioxidant enzymes can protect cells against the genotoxic damages induced by chrysotile fibers, and are highly suggestive of the roles of oxyradicals in the fibrogenic and carcinogenic mechanisms of asbestos fibers.
CT Check Tags: Animal; Human; Support, U.S. Gov't, P.H.S.
*Antioxidants: PD, pharmacology
*Asbestos, Serpentine: TO, toxicity
Catalase: PD, pharmacology
Cell Survival: DE, drug effects
Cells, Cultured
Chromosomes, Human, Pair 11
Cyclic N-Oxides: PD, pharmacology
CHO Cells
DNA: GE, genetics
DNA Primers
Gene Amplification
Hamsters
Hybrid Cells
Hypoxanthine Phosphoribosyltransferase: GE, genetics
*Mutagenesis: DE, drug effects
Mutagenicity Tests
Mutation
Superoxide Dismutase: PD, pharmacology
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 9007-49-2 (DNA)
CN EC 1.11.1.6 (Catalase); EC 1.15.1.1 (Superoxide Dismutase); EC 2.4.2.8 (Hypoxanthine Phosphoribosyltransferase); 0 (Antioxidants); 0 (Asbestos, Serpentine); **0 (Cyclic N-Oxides)**; 0 (DNA Primers)
GEN HGPRT; M1C1; S1

L151 ANSWER 16 OF 58 MEDLINE
AN 95289165 MEDLINE
DN 95289165
TI New directions for free radical cancer research and medical applications.
AU Hahn S M; **Krishna C M; Mitchell J B**
CS Radiation Biology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA..
SO ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, **(1994)** 366 241-51. Ref: 36
Journal code: 2LU. ISSN: 0065-2598.

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199509
AB The **nitroxides** are stable, low molecular weight free radical compounds which are freely membrane permeable. These properties make the **nitroxides** valuable for the study of and possible protection against oxidative stresses. It is becoming increasingly clear that oxidative stress is important to the pathogenesis of cancer as well as to the development of treatments for cancer. Several **nitroxides** have been shown to interrupt the toxicity of oxidative stress with the protection against H2O2 toxicity and possibly ischemia/reperfusion injury being of primary importance. With respect to radiation, the **nitroxides** have afforded both in vitro and in vivo protection. The redox activity of the **nitroxides** may allow for the differential activity of these agents in normal versus tumor tissues. Further study of these compounds may yield a **nitroxide** with clinical applications as well as provide insight into the mechanisms of radiation cytotoxicity. Finally, the **nitroxides** have allowed us to explore the mechanisms of action of several chemotherapeutic agents. Understanding these processes is important to the process of ameliorating the toxicity of therapies and to the rationale design of future agents.
CT Check Tags: Animal; Human
*Antioxidants: PD, pharmacology
Antioxidants: TU, therapeutic use
Cell Line
Cell Survival: DE, drug effects
***Cyclic N-Oxides: PD, pharmacology**
Free Radical Scavengers: PD, pharmacology
Free Radicals
***Neoplasms: DT, drug therapy**
***Neoplasms: PC, prevention & control**
*Radiation-Protective Agents: PD, pharmacology
Radiation-Protective Agents: TU, therapeutic use
Spin Labels
CN 0 (Antioxidants); **0 (Cyclic N-Oxides)**; 0 (Free Radical Scavengers); 0 (Free Radicals); 0 (Radiation-Protective Agents); 0 (Spin Labels)

L151 ANSWER 17 OF 58 MEDLINE
AN 95228014 MEDLINE
DN 95228014
TI Protection from radiation-induced chromosomal aberrations by the **nitroxide Tempol**.
AU Johnstone P A; DeGraff W G; **Mitchell J B**
CS Radiation Biology Branch, National Cancer Institute, Bethesda, Maryland 20892, USA..
SO CANCER, **(1995 May 1)** 75 (9) 2323-7.
Journal code: CLZ. ISSN: 0008-543X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199507
AB BACKGROUND. The **nitroxide Tempol** (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl) is a stable, free radical that exhibits protection from ionizing radiation damage and from oxidative stress mediated through exposure of cells to superoxide or hydrogen peroxide. Radiation protection has been observed in both in vivo and in vitro models. To understand the mechanism of **Tempol**-mediated radioprotection better, the production of radiation-induced chromosome aberrations was evaluated. This study analyzed **Tempol**-mediated radioprotection of human peripheral blood lymphocytes (PBLs). METHODS.

Peripheral blood lymphocytes were exposed to control (0mM), 10 mM (Tp10), and 50 mM (Tp50) concentrations of **Tempol** for 20 minutes before irradiation with 0, 150, 300, and 450 cGy. One quarter ml whole blood was cultured in F12 medium and phytohemagglutinin at 37 degrees C for 49, 54, 59, and 64 hours. Colcemide was added to each sample for the last 5 hours before harvest. Cells were harvested, treated with hypotonic solution, and fixed before dropping on cold clean slides. Mitotic indices and frequency of dicentric, ring, and triradial chromosomal aberrations were determined at 1000x magnification for each treatment group at each collection point. RESULTS. Treatment of cells with **Tempol** alone did not induce the chromosomal aberration frequency above that for unirradiated controls. Radiation dose response curves for total chromosome aberration production revealed radioprotection for **Tempol** treatment for both 10 and 50 mM exposures. **Tempol** protection factors (assessed at 0.2 aberrations/cell level) for Tp 10 and Tp 50 were 2.2 and 2.8, respectively. CONCLUSIONS. **Tempol** protects against radiation-induced chromosome aberrations in human PBLs. This finding is consistent with and lends support to previous studies in which **Tempol** was reported to enhance cell survival and reduce radiation-induced DNA double strand breaks.

CT Check Tags: Human; Male
Cell Survival: DE, drug effects
Cell Survival: RE, radiation effects
***Chromosome Aberrations**
***Chromosomes: DE, drug effects**
***Chromosomes: RE, radiation effects**
Cyclic N-Oxides: AD, administration & dosage
***Cyclic N-Oxides: PD, pharmacology**
Dose-Response Relationship, Drug
Dose-Response Relationship, Radiation
DNA: DE, drug effects
DNA: RE, radiation effects
DNA Damage
Free Radicals: AD, administration & dosage
Free Radicals: PD, pharmacology
*Lymphocytes: DE, drug effects
*Lymphocytes: RE, radiation effects
Metaphase
Mitotic Index
Radiation Dosage
Radiation-Protective Agents: AD, administration & dosage
***Radiation-Protective Agents: PD, pharmacology**
Regression Analysis

RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 9007-49-2 (DNA)

CN **0 (Cyclic N-Oxides)**; 0 (Free Radicals); 0 (Radiation-Protective Agents)

L151 ANSWER 18 OF 58 MEDLINE
AN 95137433 MEDLINE
DN 95137433
TI Modulation of streptonigrin cytotoxicity by **nitroxide** SOD mimics.
AU **Krishna M C**; Halevy R F; Zhang R; Gutierrez P L; Samuni A
CS Radiation Biology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.
SO FREE RADICAL BIOLOGY AND MEDICINE, **(1994 Nov)** 17 (5) 379-88. Journal code: FRE. ISSN: 0891-5849.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199505
AB **Nitroxides** are cell-permeable, stable radicals that react readily with paramagnetic species such as transition metals or short-lived free radicals, though not generally with diamagnetic molecules.

Nitroxides can undergo one-electron selective redox reactions and thereby potentially modify the activity of cytotoxic drugs. Streptonigrin (SN) toxicity requires bioreduction to yield the semiquinone radical, and the toxicity is reportedly mediated by transition metals and oxygen-derived reactive species via redox-cycling of the semiquinone intermediate. The present study shows that (1) **nitroxides** protected isolated DNA and also aerated or hypoxic bacterial cells from SN toxicity; (2) H2O2 potentiated the hypoxic cytotoxicity of the drug but inhibited the damage to aerated cells; (3) pretreatment of cells with H2O2 conferred some protection, but not when the drug alone was preexposed to H2O2; and (4) desferrioxamine and 2,2-dipyridyl, though neither diethylenetriamino pentaacetate, exogenous catalase, or superoxide dismutase, decreased SN-induced cell killing. The mechanisms by which **nitroxides** protect from SN toxicity involve both a selective radical-radical reaction with SN semiquinone and the reoxidation of reduced cellular transition metal ions. On the other hand, H2O2 appears to exert two opposing effects: (1) facilitation of cell killing by the Fenton reaction and (2) lowering the cellular level of reducing equivalents, thus inhibiting the bioreductive activation of SN.

CT Check Tags: Comparative Study; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.
Aerobiosis
Anaerobiosis
***Cyclic N-Oxides: PD, pharmacology**
*DNA Damage
Electron Spin Resonance Spectroscopy
*Escherichia coli: DE, drug effects
Escherichia coli: GD, growth & development
Free Radicals
Hydrogen Peroxide: TO, toxicity
Hydroxyl Radical: AN, analysis
Kinetics
Spin Labels
*Streptonigrin: TO, toxicity
***Superoxide Dismutase**
Superoxides: AN, analysis

RN 11062-77-4 (Superoxides); 14691-88-4 (tempamine); 3352-57-6 (Hydroxyl Radical); 3930-19-6 (Streptonigrin); 7722-84-1 (Hydrogen Peroxide)

CN **EC 1.15.1.1 (Superoxide Dismutase); 0 (Cyclic N-Oxides)** ; 0 (Free Radicals); 0 (Spin Labels)

L151 ANSWER 19 OF 58 MEDLINE

AN 95032187 MEDLINE

DN 95032187

TI Free radical modes of cytotoxicity of adriamycin and streptonigrin.

AU DeGraff W; Hahn S M; **Mitchell J B; Krishna M C**

CS Radiation Biology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892..

SO BIOCHEMICAL PHARMACOLOGY, **(1994 Oct 7)** 48 (7) 1427-35.
Journal code: 9Z4. ISSN: 0006-2952.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199501

AB Free radical modes of cytotoxicity of streptonigrin (STN) and Adriamycin (ADR) in Chinese hamster V79 cells under aerobic conditions were evaluated using 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (TP), a low molecular weight stable **nitroxide** free radical with antioxidant properties and desferrioxamine (DF), a transition metal chelator. In addition, exogenous superoxide dismutase (SOD, EC 1.15.1.1) and catalase (CAT, EC 1.11.1.6), were tested for cytoprotective effects. EPR studies showed that TP reacts with the semiquinones of both ADR and STN and also with O2- radicals generated during aerobic redox cycling of the respective semiquinone radicals. Pulsed field gel electrophoresis studies confirmed that DNA double-strand breaks (dsb) induced by STN in V79 cells were

inhibited completely by TP, whereas ADR-induced DNA dsb were not affected by TP. Clonogenic cell survival studies showed that STN-induced cytotoxicity could be inhibited completely by DF or TP. Both agents were ineffective in inhibiting ADR-induced cytotoxicity. SOD and CAT were ineffective in protecting against both STN and ADR cytotoxicity. Our results are consistent with a mechanism requiring the semiquinone radical intermediate of STN for cytotoxicity and minimal free radical involvement in ADR-induced V79 cell cytotoxicity.

CT Check Tags: Animal
Catalase: PD, pharmacology
Cell Line
Cell Survival: DE, drug effects
Cricetulus
Cyclic N-Oxides: AI, antagonists & inhibitors
Cyclic N-Oxides: PD, pharmacology
Deferoxamine: PD, pharmacology
Dose-Response Relationship, Drug
*Doxorubicin: PD, pharmacology
DNA Damage
Electron Spin Resonance Spectroscopy
Free Radicals
Hamsters
NADH Dehydrogenase
Quinones: CH, chemistry
Spin Labels
Streptonigrin: AI, antagonists & inhibitors
*Streptonigrin: PD, pharmacology
Superoxide Dismutase: PD, pharmacology

RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 23214-92-8 (Doxorubicin); 3930-19-6 (Streptonigrin); 70-51-9 (Deferoxamine)

CN EC 1.11.1.6 (Catalase); **EC 1.15.1.1 (Superoxide Dismutase)**; EC 1.6.99.3 (NADH Dehydrogenase); **0 (Cyclic N-Oxides)**; 0 (Free Radicals); 0 (Quinones); 0 (Spin Labels)

L151 ANSWER 20 OF 58 MEDLINE

AN 94338702 MEDLINE

DN 94338702

TI Selective potentiation of NMDA-induced neuronal injury following induction of astrocytic iNOS.

AU Hewett S J; Csernansky C A; Choi D W

CS Department of Neurology, Washington University School of Medicine, St. Louis, Missouri 63110..

NC DA 07261 (NIDA)
NS 07027 (NINDS)
NS 30337 (NINDS)

SO NEURON, **(1994 Aug)** 13 (2) 487-94.
Journal code: AN8. ISSN: 0896-6273.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199411

AB Nitric oxide (NO) produced by the constitutive NO synthase (cNOS) in neurons has been implicated in mediating excitotoxic neuronal death. In our murine cortical cell culture system, NMDA neurotoxicity was not blocked by addition of the NOS inhibitors, NG-nitro-L-arginine or aminoguanidine. However, following activation of inducible NOS in astrocytes by interleukin-1 beta plus interferon-gamma, NMDA but not kainate neurotoxicity was markedly potentiated. This selective potentiation of NMDA neurotoxicity was blocked by NOS inhibition or antioxidants (superoxide dismutase/catalase or **Tempol**) and could be mimicked by NO generators (SIN-1 or SNAP) or the oxygen radical generator, pyragallol. These results raise the possibility that NO production by astrocytes may contribute to NMDA receptor-mediated neuronal death, perhaps through interaction with oxygen radicals.

CT Check Tags: Animal; In Vitro; Support, U.S. Gov't, P.H.S.

*Amino Acid Oxidoreductases: PH, physiology
*Astrocytes: EN, enzymology
Cell Death: DE, drug effects
Cells, Cultured
Drug Synergism
Enzyme Induction
Interferon Type II: PD, pharmacology
Interleukin-1: PD, pharmacology
Kainic Acid: TO, toxicity
Mice
Molsidomine: AA, analogs & derivatives
Molsidomine: PD, pharmacology
N-Methylaspartate: TO, toxicity
*Neurons: DE, drug effects
Nitric Oxide: PH, physiology
Penicillamine: AA, analogs & derivatives
Penicillamine: PD, pharmacology
RN 10102-43-9 (Nitric Oxide); 25717-80-0 (Molsidomine); 33876-97-0 (CV 664); 487-79-6 (Kainic Acid); 52-67-5 (Penicillamine); 6384-92-5 (N-Methylaspartate); 79032-48-7 (S-nitroso-N-acetylpenicillamine); 82115-62-6 (Interferon Type II)
CN EC 1.14.13.39 (Nitric-Oxide Synthase); EC 1.4. (Amino Acid Oxidoreductases); 0 (Interleukin-1)

L151 ANSWER 21 OF 58 MEDLINE
AN 94335598 MEDLINE
DN 94335598
TI Measurement of the intracellular concentration of oxygen in a cell perfusion system.
AU Chen K; Ng C E; Zweier J L; Kuppusamy P; Glickson J D; Swartz H M
CS Department of Radiology and Radiological Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland.
NC GM 34250 (NIGMS)
CA 51935 (NCI)
51950
+
SO MAGNETIC RESONANCE IN MEDICINE, **(1994 Jun)** 31 (6) 668-72.
Journal code: MHR. ISSN: 0740-3194.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199411
AB [O2] was measured in the embedding material (alginate) in a typical apparatus for conducting studies of viable cells with NMR, using low frequency EPR. In suspension cultures respiration was independent of [O2] in the perfusing media down to about 1 microM while in alginate beads, the comparable value was 70 microM, indicating that the alginate was a very substantial barrier to the free diffusion of oxygen. With knowledge of [O2] in the various compartments, [O2] in the perfusing medium can be increased and the full power of NMR can be used to provide information on metabolism under various conditions. These results also provide evidence supporting the feasibility and usefulness of EPR techniques using **nitroxides** to measure [O2] in macroscopic samples such as NMR perfusion tubes. This technique is rapid, apparently nonperturbing, and enables one to differentiate between the concentrations of oxygen in different compartments.
CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Alginates
Cell Count
Culture Media
Cyclic N-Oxides: DU, diagnostic use
Diffusion
*Electron Spin Resonance Spectroscopy: MT, methods
Extracellular Space: ME, metabolism
Fibrosarcoma: ME, metabolism

Fibrosarcoma: PA, pathology
Kinetics
Mice
*Nuclear Magnetic Resonance: MT, methods
Oxygen: AD, administration & dosage
*Oxygen: AN, analysis
*Oxygen Consumption
Spin Labels
Surface Properties
Tumor Cells, Cultured
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 7782-44-7 (Oxygen); 9005-32-7 (alginic acid)
CN 0 (Alginates); 0 (Culture Media); **0 (Cyclic N-Oxides)**; 0 (Spin Labels)

L151 ANSWER 22 OF 58 MEDLINE
AN 94268224 MEDLINE
DN 94268224
TI Pharmacokinetic properties of **nitroxide**-labeled albumin in mice.
AU Liebmann J; Bourg J; **Krishna C M**; Glass J; Cook J A; **Mitchell J B**
CS Radiation Biology Branch, National Cancer Institute, Bethesda, MD 20892..
SO LIFE SCIENCES, **(1994)** 54 (26) PL503-9.
Journal code: L62. ISSN: 0024-3205.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199409
AB We have conjugated bovine serum albumin (BSA) with a pyrrolidinyl **nitroxide** and report on the in vivo pharmacokinetic properties of this conjugate in mice. In vivo EPR measurements of **nitroxide** were obtained after intravenous injection of 30 mg of labeled BSA by analysis of the **nitroxide** signal from the tails of mice. Following in vivo **nitroxide** measurements, the animals were sacrificed by exsanguination and organs were removed for determination of **nitroxide** levels. The level of **nitroxide** as determined by in vivo measurements declined exponentially with time and had a half-life (t1/2) of 7 hours. Blood **nitroxide** levels also declined exponentially with time with an initial t1/2 of 70 minutes and a terminal t1/2 of 10 hours. **Nitroxide** concentration varied among different organs; no **nitroxide** was detected within brain whereas lung had high concentrations of **nitroxide**. Liver and kidney both had relatively low levels of oxidized **nitroxide**, though total **nitroxide** (reduced plus oxidized) accumulated in the kidneys with time. **Nitroxide**-labeled BSA was well tolerated by the mice, is relatively stable, and is mainly confined to the intravascular space. **Nitroxide**-labeled albumin may be useful as a contrast agent for MRI or EPR imaging.
CT Check Tags: Animal; Comparative Study; Female
Brain: ME, metabolism
Cyclic N-Oxides: AD, administration & dosage
***Cyclic N-Oxides: ME, metabolism**
Electron Spin Resonance Spectroscopy
Half-Life
Injections, Intravenous
Lung: ME, metabolism
Mice
Mice, Inbred C3H
Serum Albumin, Bovine: AD, administration & dosage
*Serum Albumin, Bovine: ME, metabolism
Tissue Distribution
CN **0 (Cyclic N-Oxides)**; 0 (Serum Albumin, Bovine)

L151 ANSWER 23 OF 58 MEDLINE
AN 94252918 MEDLINE

DN 94252918
TI Bioreductive metabolism of SR-4233 (WIN 59075) by whole cell suspensions under aerobic and hypoxic conditions: role of the pentose cycle and implications for the mechanism of cytotoxicity observed in air.
AU Tuttle S W; Hazard L; Koch C J; **Mitchell J B**; Coleman C N; Biaglow J E
CS University of Pennsylvania School of Medicine, Philadelphia 19104..
NC CA-44982 (NCI)
CA-09677 (NCI)
SO INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS, **(1994 May 15)** 29 (2) 357-62.
Journal code: G97. ISSN: 0360-3016.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199409
AB PURPOSE: Measurement of pentose cycle (PC) activity is shown to be a noninvasive means for monitoring the reduction of SR-4233 in whole cells. Comparing these measurements to the actual measurements of drug loss under aerobic and hypoxic conditions helps to define the mechanism for the associated aerobic toxicity. METHODS AND MATERIALS: SR-4233 is activated to a toxic species by bioreductive metabolism. NADPH is required for the activation of the drug by purified enzymes, cell homogenates and whole cells. In vivo the NADPH:NADP+ ratio is maintained by the oxidation of glucose via the oxidative limb of the pentose cycle. By measuring radiolabeled 14CO2 released as a product of this oxidation one can get an accurate measurement of the rate of drug metabolism in whole cells. These results are compared to measurements of drug consumption under aerobic and hypoxic conditions using an HPLC assay. RESULTS: SR-4233 stimulates pentose cycle activity to a greater extent in air then under hypoxia, however, in the presence of added catalase, pentose cycle activity is stimulated to a similar extent under both conditions. The higher levels of PC activity observed in air are due to the production of hydrogen peroxide by the **nitroxide** free radical undergoing futile redox cycling.
The contribution of H2O2 to the observed aerobic cytotoxicity of SR-4233 is minimal however, since toxicity is only slightly reduced in the presence of exogenous catalase and antioxidants such as vitamin E. The level of PC stimulation by SR-4233 suggests that the rate of electron addition to the drug is independent of O2 concentration. The loss of drug from the incubation medium, i.e., conversion to a stable intermediate species, occurs approximately five times faster under nitrogen than in air for A549 cells. It is the rate of drug loss from the cell and not the rate of reduction which best correlates with the observed aerobic and hypoxic toxicity. CONCLUSION: Toxicity in air and in nitrogen is directly related to the rate of drug reduction, i.e., at equivalent levels of drug loss we observe equal levels of cytotoxicity.
CT Check Tags: Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Aerobiosis
*Antineoplastic Agents: ME, metabolism
Cells, Cultured
Hydrogen Peroxide: ME, metabolism
NADP: ME, metabolism
Oxidation-Reduction
*Pentosephosphate Pathway
*Radiation-Sensitizing Agents: ME, metabolism
Suspensions
*Triazines: ME, metabolism
RN 27314-97-2 (tirapazamine); 53-59-8 (NADP); 7722-84-1 (Hydrogen Peroxide)
CN 0 (Antineoplastic Agents); 0 (Radiation-Sensitizing Agents); 0 (Suspensions); 0 (Triazines)

L151 ANSWER 24 OF 58 MEDLINE
AN 94252906 MEDLINE
DN 94252906
TI Modification of the aerobic cytotoxicity of etanidazole.

AU Palayoor S T; Bump E A; Malaker K; Langley R E; Saroff D M; Delfs J R; Hurwitz S J; Coleman C N
CS Joint Center for Radiation Therapy, Harvard Medical School, Boston, MA 02115.
NC CA 42391 (NCI)
SO INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS, **(1994 May 15)** 29 (2) 289-93.
Journal code: G97. ISSN: 0360-3016.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199409
AB PURPOSE: To determine the feasibility of modifying the aerobic cytotoxicity of etanidazole without interfering with the tumoricidal action of radiation plus etanidazole. METHODS AND MATERIALS: The aerobic cytotoxicity of etanidazole was studied using two different models: (1) Induction of apoptosis in EL4 cells: apoptotic DNA fragmentation was analyzed by agarose gel electrophoresis following 24 h treatment with etanidazole alone or in combination with various modifiers. (2) Spinal cord neuronal loss in organotypic roller tube cultures: Survival of acetylcholinesterase positive ventral horn neurons was analyzed morphometrically following 72 h treatment with etanidazole alone or in combination with vitamin E succinate. RESULTS: Etanidazole (10 mM) induced apoptosis in EL4 cells. This effect was suppressed by 24 h treatment with TPA, IBMX, the free radical scavenger **TEMPOL** or vitamin E succinate. Vitamin E succinate also protected spinal cord cultures from etanidazole-induced neuronal loss. CONCLUSION: These results suggest that it might be possible to modify the neurotoxicity of etanidazole with agents that would not be expected to interfere with the tumoricidal action of radiation plus etanidazole.
CT Check Tags: Animal; Support, U.S. Gov't, P.H.S.
Aerobiosis
Apoptosis
Calcium: ME, metabolism
Cell Survival: DE, drug effects
*Etanidazole: PD, pharmacology
Lymphoma, T-Cell: PA, pathology
Mice
Superoxides: ME, metabolism
Tumor Cells, Cultured
Vitamin E: AA, analogs & derivatives
Vitamin E: PD, pharmacology
RN 11062-77-4 (Superoxides); 1406-18-4 (Vitamin E); 17407-37-3 (vitamin E succinate); 22668-01-5 (Etanidazole); 7440-70-2 (Calcium)

L151 ANSWER 25 OF 58 MEDLINE
AN 94195930 MEDLINE
DN 94195930
TI Protection from lethal irradiation by the combination of stem cell factor and **tempol**.
AU Liebmann J; **DeLuca A M**; Epstein A; Steinberg S M; Morstyn G; **Mitchell J B**
CS Radiobiology Section, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892..
SO RADIATION RESEARCH, **(1994 Mar)** 137 (3) 400-4.
Journal code: QMP. ISSN: 0033-7587.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199407
AB Cytokines that stimulate growth and differentiation of hematopoietic precursor cells have been used as protectors in vivo against ionizing radiation. Recently, we have shown that the **nitroxide tempol** is also an effective radiation protector in vivo. The

purpose of the present study was to determine if the combination of **tempol** with stem cell factor (SCF, c-kit ligand) would provide enhanced radiation protection in C57 mice compared with the protection afforded by either agent alone. Mice were exposed to whole-body irradiation and assessed for survival at 30 days after irradiation. No control mice survived doses of more than 9 Gy. Treatment of mice before and after radiation with SCF alone (100 micrograms/kg at -20 h, -4 h and +4 h) protected mice from radiation at doses of as high as 10 Gy (76% survival). **Tempol** (350 mg/kg) given 10 min prior to radiation was a radioprotector at 9 Gy (55% survival). The combination of SCF and **tempol** increased the survival of mice exposed to radiation doses up to 11 Gy (32% survival for the combination vs 4% for SCF alone and 0% for **tempol** alone; P < 0.001 for the combination vs either agent alone). Lower doses of SCF alone (1 microgram/kg) or **tempol** alone (275 mg/kg) did not protect mice from radiation. However, the combination of these reduced doses of SCF and **tempol** protected mice from lethal irradiation at 10 Gy. Stem cell factor and **tempol** given either singly or together were well tolerated by the animals. These data show that SCF and **tempol** are radiation protectors and that their radioprotective effects are more than additive when the agents are given together.

CT Check Tags: Animal; Female
***Cyclic N-Oxides: PD, pharmacology**
Drug Synergism
Gamma Rays
*Hematopoietic Cell Growth Factors: PD, pharmacology
Mice
Mice, Inbred C57BL
***Radiation-Protective Agents: PD, pharmacology**
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**
CN **0 (Cyclic N-Oxides)**; 0 (Hematopoietic Cell Growth Factors); 0 (Radiation-Protective Agents); 0 (Stem Cell Factor)

L151 ANSWER 26 OF 58 MEDLINE
AN 94192631 MEDLINE
DN 94192631
TI Polymerase chain reaction-directed DNA sequencing of bleomycin-induced "nondeletion"-type, 6-thioguanine-resistant mutants in Chinese hamster ovary cell derivative AS52: effects of an inhibitor and a mimic of superoxide dismutase.
AU An J; Hsie A W
CS Department of Preventive Medicine and Community Health, University of Texas Medical Branch, Galveston 77555-1010..
NC 1RO1CA56434-01 (NCI)
SO ENVIRONMENTAL AND MOLECULAR MUTAGENESIS, **(1994)** 23 (2) 101-9.
Journal code: EMM. ISSN: 0893-6692.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199407
AB Bleomycin-induced, 6-thioguanine-resistant, "non deletion" mutants pretreated with or without either TRIEN (triethylenetetramine), a superoxide dismutase (SOD) inhibitor, or **TEMPOL** (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl), a SOD mimic, were analyzed by polymerase chain reaction (PCR)-directed DNA sequencing in a Chinese hamster ovary (CHO) cell derivative, AS52. Among the 23 bleomycin-induced mutants, six have 3-bp 5'-TGA-3' deletions in the region of 366-371, five have single-base deletions, seven have base substitutions, three have insertions, and two have possible translocations. Among the 16 bleomycin-induced mutants pretreated with TRIEN, six have the 5'-TGA-3' deletion (366-371), two have single-base deletions, one has a 13-bp deletion, four have single-base substitutions, one has a double-base substitution, and two have insertions. Among the 17 bleomycin-induced mutants pretreated with **TEMPOL**, six have the same TGA deletions, two have single-base deletions, two have single-base

insertions, four have single-base substitutions, one mutant has a 12-bp deletion, one has a 13-bp deletion, and one mutant shows no detectable change in its coding region in the DNA sequence. A possible shift from a ROS-mediated mutational spectrum to a spontaneous mutational spectrum by TRIEN further indicates that reactive oxygen species play an important role in bleomycin mutagenesis in mammalian cells.

CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Base Sequence
*Bleomycin: TO, toxicity
***Cyclic N-Oxides: PD, pharmacology**
CHO Cells
DNA
*DNA Mutational Analysis
Frameshift Mutation
Hamsters
Molecular Sequence Data
Oxidation-Reduction
Pentosyltransferases: GE, genetics
Polymerase Chain Reaction
Sequence Analysis, DNA
Sequence Deletion
Superoxide Dismutase: AI, antagonists & inhibitors
Superoxide Dismutase: DE, drug effects
*Superoxide Dismutase: ME, metabolism
Thioguanine: PD, pharmacology
*Triethylenetetramine: PD, pharmacology

RN 11056-06-7 (Bleomycin); 112-24-3 (Triethylenetetramine); 154-42-7 (Thioguanine); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 9007-49-2 (DNA)

CN EC 1.15.1.1 (Superoxide Dismutase); EC 2.4.2. (Pentosyltransferases); EC 2.4.2.22 (xanthine phosphoribosyltransferase); **0 (Cyclic N-Oxides)**

GEN gpt

L151 ANSWER 27 OF 58 MEDLINE

AN 94185063 MEDLINE

DN 94185063

TI Potential use of **nitroxides** in radiation oncology.

AU Hahn S M; **Krishna C M**; Samuni A; DeGraff W; Cuscela D O; Johnstone P; **Mitchell J B**

CS Radiation Biology Section, National Cancer Institute, NIH, Bethesda, Maryland 20892.

SO CANCER RESEARCH, **(1994 Apr 1)** 54 (7 Suppl) 2006s-2010s. Ref: 43
Journal code: CNF. ISSN: 0008-5472.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LA English

FS Priority Journals; Cancer Journals

EM 199406

AB The identification of radioprotectors is an important goal for those involved in radiation oncology and for those interested in the investigation of the mechanisms of radiation cytotoxicity. Recently, a new class of in vitro and in vivo radioprotectors, the **nitroxides**, has been discovered. The **nitroxides** are low-molecular-weight stable free radicals which are freely membrane permeable and which have been shown to act as superoxide dismutase mimics. Further investigation of these compounds has shown that a water-soluble **nitroxide**, **Tempol**, protects cultured Chinese hamster V79 cells from the cytotoxicity caused by superoxide, hydrogen peroxide, and t-butyl hydroperoxide. **Tempol** and five other water-soluble **nitroxides** have also been shown to protect V79 cells against radiation-induced cytotoxicity. Potential mechanisms of protection by the **nitroxides** include oxidation of reduced transition metals, superoxide dismutase-like activity, and scavenging of oxy- and

carbon-based free radicals. In vivo studies reveal that **Tempol** protects C3H mice from the lethal effects of radiation with a dose causing 50% lethality within 30 days of 9.97 Gy and 7.84 Gy in **Tempol** -treated and saline-treated mice, respectively, and a dose modification factor of 1.3. The **nitroxides** represent a new class of non-thiol radioprotectors which may also have application as general antioxidants. Additional work is necessary to screen other **nitroxides** for in vivo radioprotection and toxicity as well as to fully evaluate the extent to which these compounds protect tumors.

CT Check Tags: Animal
Cell Line
Cell Survival: DE, drug effects
*Cell Survival: RE, radiation effects
Cricetulus
***Cyclic N-Oxides: PD, pharmacology**
Cyclic N-Oxides: TU, therapeutic use
*Cytotoxins: TO, toxicity
Dose-Response Relationship, Radiation
Hamsters
Hydrogen Peroxide: TO, toxicity
Mice
Mice, Inbred C3H
Peroxides: TO, toxicity
***Radiation-Protective Agents: PD, pharmacology**
Radiation-Protective Agents: TU, therapeutic use
Superoxides: TO, toxicity

RN 11062-77-4 (Superoxides); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 75-91-2 (tert-Butylhydroperoxide); 7722-84-1 (Hydrogen Peroxide)

CN **0 (Cyclic N-Oxides)**; 0 (Cytotoxins); 0 (Peroxides); 0 (Radiation-Protective Agents)

L151 ANSWER 28 OF 58 MEDLINE
AN 93390545 MEDLINE
DN 93390545
TI Polymerase chain reaction-based deletion screening of bleomycin induced 6-thioguanine-resistant mutants in Chinese hamster ovary cells: the effects of an inhibitor and a mimic of superoxide dismutase.
AU An J; Hsie A W
CS Department of Preventive Medicine and Community Health, University of Texas Medical Branch, Galveston 77555-1010.
SO MUTATION RESEARCH, **(1993 Oct)** 289 (2) 215-22.
Journal code: NNA. ISSN: 0027-5107.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199312
AB Bleomycin-induced 6-thioguanine-resistant mutants pretreated with or without TRIEN (triethylenetetramine), a superoxide dismutase (SOD) inhibitor, or **TEMPOL** (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl), an SOD mimic, were analyzed by polymerase chain reaction (PCR)-based deletion screening in a Chinese hamster ovary (CHO) clone K1-BH4 and its derivative AS52 cells. As we proposed earlier, TRIEN would decrease and **TEMPOL** would increase the intracellular level of hydroxyl radical leading to a higher and lower recovery of deletion mutants. We found that the proportion of the deletion mutants induced by bleomycin at the hypoxanthine-guanine phosphoribosyltransferase (hprt) locus in K1-BH4 cells was 45.5% (25/55). The proportion of deletion HPRT- mutants induced by bleomycin pretreated with TRIEN was 31.0% (9/29) and with **TEMPOL** was 50.0% (14/28). The proportion of deletion mutants induced by bleomycin on the xanthine-guanine phosphoribosyltransferase (gpt) gene in AS52 cells was 61.0% (36/59). The proportion of deletion GPT- mutants induced by bleomycin pretreated with TRIEN was 56.8% (21/37) and with **TEMPOL** was 61.4% (27/44). The trend of the change of the proportion of bleomycin-induced deletion

mutants as affected by TRIEN and by **TEMPOL** provides molecular evidence for the involvement of reactive oxygen species (ROS) in bleomycin mutagenesis in mammalian cells, in which deletion is a major type of induced mutation.

CT Check Tags: Animal; Support, Non-U.S. Gov't
Base Sequence
*Bleomycin: TO, toxicity
Cricetulus
Cyclic N-Oxides: PD, pharmacology
CHO Cells
DNA Mutational Analysis
Hamsters
Hypoxanthine Phosphoribosyltransferase: GE, genetics
Molecular Sequence Data
*Mutagenesis
Pentosyltransferases: GE, genetics
Polymerase Chain Reaction
*Reactive Oxygen Species: ME, metabolism
*Sequence Deletion
Superoxide Dismutase: AI, antagonists & inhibitors
*Superoxide Dismutase: ME, metabolism
Thioguanine: PD, pharmacology
Triethylenetetramine: PD, pharmacology

RN 11056-06-7 (Bleomycin); 112-24-3 (Triethylenetetramine); 154-42-7 (Thioguanine); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**

CN EC 1.15.1.1 (Superoxide Dismutase); EC 2.4.2. (Pentosyltransferases); EC 2.4.2.22 (xanthine phosphoribosyltransferase); EC 2.4.2.8 (Hypoxanthine Phosphoribosyltransferase); **0 (Cyclic N-Oxides)**; 0 (Reactive Oxygen Species)

L151 ANSWER 29 OF 58 MEDLINE
AN 93380687 MEDLINE
DN 93380687
TI The effect of oxygen at physiological levels on the detection of free radical intermediates by electron paramagnetic resonance.
AU **Krishna M C**; Samuni A
CS Radiation Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892..
SO FREE RADICAL RESEARCH COMMUNICATIONS, **(1993)** 18 (4) 239-47.
Journal code: FRR. ISSN: 8755-0199.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199312
AB It is well known that oxygen enhances the relaxation of free radical EPR probes through spin lattice and Heisenberg spin-spin interactions with consequent effect on the line height and width. The two relaxation processes have opposing effects on the signal heights and depend on the concentration of oxygen, the incident microwave power, and the presence of other paramagnetic species. During EPR studies of chemical, biochemical, and cellular processes involving free radicals, molecular oxygen has significant magnetic influence on the EPR signal intensity of the free radical species under investigation in addition to affecting the rates of production of the primary species and the stability of the spin adduct **nitroxides**. These effects are often overlooked and can cause artifacts and lead to erroneous interpretation. In the present study, the effects of oxygen and ferricyanide on the EPR signal height of stable and persistent spin adduct **nitroxides** at commonly employed microwave powers were examined. The results show that under commonly adopted EPR spectrometer instrumental conditions, artifactual changes in the EPR signal of spin adducts occur and the best way to avoid them is by keeping the oxygen level constant using a gas-permeable cell.
CT Check Tags: Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.
Cyclic N-Oxides: ME, metabolism

*Electron Spin Resonance Spectroscopy
Ferricyanides: PD, pharmacology
Free Radicals
Microwaves
Oxygen: AD, administration & dosage
*Oxygen: PD, pharmacology
Spin Labels
Triacetoneamine-N-Oxyl: ME, metabolism
RN 13408-62-3 (hexacyanoferrate III); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; **2564-83-2 (TEMPO)**; 2896-70-0 (Triacetoneamine-N-Oxyl); 3317-61-1 (5,5-dimethyl-1-pyrroline-1-oxide); 7782-44-7 (Oxygen)
CN **0 (Cyclic N-Oxides)**; 0 (Ferricyanides); 0 (Free Radicals); 0 (Spin Labels)

L151 ANSWER 30 OF 58 MEDLINE
AN 93285696 MEDLINE
DN 93285696
TI Study of photodynamic reactions of p-nitroacetophenone using ESR and optical techniques.
AU **Krishna C M**; Roy A K
CS Solid State & Molecular Physics Division, Saha Institute of Nuclear Physics, Bidhan Nagar, Calcutta..
SO INDIAN JOURNAL OF BIOCHEMISTRY AND BIOPHYSICS, **(1993 Feb)** 30 (1) 7-9.
Journal code: GHW. ISSN: 0301-1208.
CY India
DT Journal; Article; (JOURNAL ARTICLE)
LA English
EM 199309
AB The photosensitizing properties of p-nitroacetophenone (PNAP), a well-known radiosensitizer, have been studied in near UV region. The mechanism of PNAP photosensitization has been investigated by testing the efficiency of singlet oxygen production using photooxidation of 2,2,6,6-tetramethylpiperidine (TEMP) and photodegradation of guanosine. In both the cases, the enhancement effect of deuterated solvents has been observed. Results of these experiments suggest the significant role of type II mechanisms in PNAP photosensitization.
CT Check Tags: In Vitro; Support, Non-U.S. Gov't
Acetophenones: CH, chemistry
*Acetophenones: RE, radiation effects
Cyclic N-Oxides: RE, radiation effects
Electron Spin Resonance Spectroscopy
Guanosine: RE, radiation effects
Oxygen: RE, radiation effects
Photochemistry
Radiation-Sensitizing Agents: CH, chemistry
*Radiation-Sensitizing Agents: RE, radiation effects
Spectrophotometry, Ultraviolet
Spin Labels
RN 100-19-6 (4-nitroacetophenone); 118-00-3 (Guanosine); 17778-80-2 (singlet oxygen); **2564-83-2 (TEMPO)**; 7782-44-7 (Oxygen)
CN 0 (Acetophenones); **0 (Cyclic N-Oxides)**; 0 (Radiation-Sensitizing Agents); 0 (Spin Labels)

L151 ANSWER 31 OF 58 MEDLINE
AN 93093491 MEDLINE
DN 93093491
TI **Nitroxide**-mediated protection against X-ray- and neocarzinostatin-induced DNA damage.
AU DeGraff W G; **Krishna M C**; Kaufman D; **Mitchell J B**
CS Radiobiology Section, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.
SO FREE RADICAL BIOLOGY AND MEDICINE, **(1992 Nov)** 13 (5) 479-87.
Journal code: FRE. ISSN: 0891-5849.
CY United States

DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199303
AB The stable free radical **Tempol** (4-hydroxy-2,2,6,6-tetramethyl-piperidinyloxy) has been shown to protect against X-ray-induced cytotoxicity and hydrogen peroxide- or xanthine oxidase-induced cytotoxicity and mutagenicity. The ability of **Tempol** to protect against X-ray- or neocarzinostatin (NCS)-induced mutagenicity or DNA double-strand breaks (dsb) was studied in Chinese hamster cells. **Tempol** (50 mM) provided a protection factor of 2.7 against X-ray-induced mutagenicity in Chinese hamster ovary (CHO) AS52 cells, with a protection factor against cytotoxicity of 3.5. Using the field inversion gel electrophoresis technique of measuring DNA dsb, 50 mM **Tempol** provides a threefold reduction in DNA damage at an X-ray dose of 40 Gy. For NCS-induced damage, **Tempol** increased survival from 9% to 80% at 60 ng/mL NCS and reduced mutation induction by a factor of approximately 3. DNA dsb were reduced by a factor of approximately 7 at 500 ng/mL NCS. **Tempol** is representative of a class of stable **nitroxide** free radical compounds that have superoxide dismutase-mimetic activity, can oxidize metal ions such as ferrous iron that are complexed to DNA, and may also detoxify radiation-induced organoperoxide radicals by competitive scvenging. The NCS chromophore is reduced by sulfhydryls to an active form. Electron spin resonance (ESR) spectroscopy shows that 2-mercaptoethanol-activated NCS reacts with **Tempol** 3.5 times faster than does unactivated NCS. Thus, **Tempol** appears to inactivate the NCS chromophore before a substantial amount of DNA damage occurs.
CT Check Tags: Animal
Cell Line
Cell Survival: DE, drug effects
*Cell Survival: RE, radiation effects
***Cyclic N-Oxides: PD, pharmacology**
CHO Cells
Dose-Response Relationship, Drug
Dose-Response Relationship, Radiation
*DNA: DE, drug effects
*DNA: RE, radiation effects
*DNA Damage
Hamsters
Kinetics
Mutagenesis
***Radiation-Protective Agents: PD, pharmacology**
X-Rays
*Zinostatin: PD, pharmacology
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 9007-49-2 (DNA); 9014-02-2 (Zinostatin)
CN **0 (Cyclic N-Oxides)**; 0 (Radiation-Protective Agents)

L151 ANSWER 32 OF 58 MEDLINE
AN 93029246 MEDLINE
DN 93029246
TI Identification of **nitroxide** radioprotectors.
AU Hahn S M; Wilson L; **Krishna C M**; Liebmann J; DeGraff W; Gamson J; Samuni A; Venzon D; **Mitchell J B**
CS Radiobiology Section, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892..
SO RADIATION RESEARCH, **(1992 Oct)** 132 (1) 87-93.
Journal code: QMP. ISSN: 0033-7587.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199301
AB The **nitroxide Tempol**, a stable free radical, has recently been shown to protect mammalian cells against several forms of

oxidative stress including radiation-induced cytotoxicity. To extend this observation, six additional water-soluble **nitroxides** with different structural features were evaluated for potential radioprotective properties using Chinese hamster V79 cells and clonogenic assays. **Nitroxides** (10 mM) were added 10 min prior to radiation exposure and full radiation dose-response curves were determined. In addition to **Tempol**, five of the six **nitroxides** afforded in vitro radioprotection. The best protectors were found to be the positively charged **nitroxides**, Tempamine and 3-aminomethyl-PROXYL, with protection factors of 2.3 and 2.4, respectively, compared with **Tempol**, which had a protection factor of 1.3. 3-Carboxy-PROXYL, a negatively charged **nitroxide**, provided minimal protection. DNA binding characteristics as studied by nonequilibrium dialysis of DNA with each of the **nitroxides** demonstrated that Tempamine and 3-amino-methyl-PROXYL bound more strongly to DNA than did **Tempol** . Since DNA is assumed to be the target of radiation-induced cytotoxicity, differences in protection may be explained by variabilities in affinity of the protector for the target. This study establishes **nitroxides** as a general class of new nonthiol radioprotectors and suggests other parameters that may be exploited to find even better **nitroxide** -induced radioprotection.

CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.
Cell Line
Cell Survival: DE, drug effects
Cell Survival: RE, radiation effects
***Cyclic N-Oxides**
***Cyclic N-Oxides: PD, pharmacology**
Dose-Response Relationship, Radiation
Hamsters
Protein Synthesis Inhibitors: PD, pharmacology
*Pyrrolidines
Pyrrolidines: PD, pharmacology
***Radiation-Protective Agents: PD, pharmacology**
Spin Labels
*Triacetoneamine-N-Oxyl
Triacetoneamine-N-Oxyl: PD, pharmacology

RN 14691-88-4 (tempamine); 2154-68-9 (2,2,5,5-tetramethyl-1-pyrrolidinyloxy-3-carboxylic acid); 2154-70-3 (3-cyano-2,2,5,5-tetramethyl-1-pyrrolidinyl-N-oxyl); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl);** 2896-70-0 (Triacetoneamine-N-Oxyl); 4399-80-8 (3-carbamoyl-2,2,5,5-tetramethyl-1-pyrrolidinyl-N-oxyl); 54606-49-4 (3-aminomethyl-2,2,5,5-tetramethyl-1-pyrrolidinyl-N-oxyl)

CN **0 (Cyclic N-Oxides);** 0 (Protein Synthesis Inhibitors); 0 (Pyrrolidines); 0 (Radiation-Protective Agents); 0 (Spin Labels)

L151 ANSWER 33 OF 58 MEDLINE

AN 92351276 MEDLINE

DN 92351276

TI Spin trap salvage from endotoxemia: the role of cytokine down-regulation.

AU Pogrebniak H W; Merino M J; Hahn S M; **Mitchell J B;** Pass H I

CS Thoracic Oncology Section, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892..

SO SURGERY, **(1992 Aug)** 112 (2) 130-9; discussion 138-9.
Journal code: VC3. ISSN: 0039-6060.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 199211

AB BACKGROUND. The spin trap alpha-phenyl-N-tert-butyl-nitrone (PBN) affords protection from the lethality of septic (lipopolysaccharide) shock. We hypothesized that PBN may work through down-regulation of the sepsis-induced cytokine cascade. METHODS. C3H/HEN mice received 30 mg/kg lipopolysaccharide 15 minutes after pretreatment with PBN or vehicle. Animals were monitored for differences in behavior, histopathologic

studies, survival, and serum levels of tumor necrosis factor (TNF-alpha), interferon-gamma (IFN-gamma), and interleukin-6 (IL-6) after lipopolysaccharide. Northern blot analyses of TNF, IFN-gamma, c-fos, and IL-6 transcripts were also performed. RESULTS. Seventy-two-hour survival was significantly higher in the PBN-treated (59/60) compared with the saline-treated animals (13/60; p2 less than 0.005), and the PBN group exhibited a blunted endotoxemic response. TNF levels were significantly lower in the PBN-treated animals at 1 to 6 hours, whereas IFN-gamma levels were depressed at 8 hours. PBN down-regulated TNF transcription at 30 minutes, with maximum lowering of all cytokine transcripts at 6 hours. PBN depressed c-fos transcription within 15 minutes of lipopolysaccharide injection. CONCLUSIONS. Spin trap protection from endotoxemia may be related to interruption of the cytokine network, with profound effects on transcription and protein elaboration. Such compounds may prove useful in not only sepsis but also other cytokine-free radical-related pathophysiologic alterations.

CT Check Tags: Animal
Arginine: PD, pharmacology
Blood Proteins: ME, metabolism
Blotting, Northern
Cytokines: BL, blood
Cytokines: GE, genetics
*Cytokines: ME, metabolism
*Down-Regulation (Physiology)
*Endotoxins: BL, blood
Intestines: DE, drug effects
Intestines: PA, pathology
Mice
Mice, Inbred C3H
Mice, Nude
Mortality
Nitrogen Oxides: ME, metabolism
***Nitrogen Oxides: PD, pharmacology**
Sodium Chloride: PD, pharmacology
*Spin Labels
Transcription, Genetic

RN 3376-24-7 (phenyl-N-tert-butylnitrone); 7004-12-8 (Arginine); 7647-14-5 (Sodium Chloride)

CN 0 (Blood Proteins); 0 (Cytokines); 0 (Endotoxins); **0 (Nitrogen Oxides)**; 0 (Spin Labels)

L151 ANSWER 34 OF 58 MEDLINE

AN 92302278 MEDLINE

DN 92302278

TI Oxoammonium cation intermediate in the **nitroxide**-catalyzed dismutation of superoxide.

AU **Krishna M C**; Grahame D A; Samuni A; **Mitchell J B**; **Russo A**

CS Radiation Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.

SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1992 Jun 15)** 89 (12) 5537-41.
Journal code: PV3. ISSN: 0027-8424.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199209

AB Dismutation of superoxide has been shown previously to be catalyzed by stable **nitroxide** compounds. In the present study, the mechanism of superoxide (.O2-) dismutation by various five-membered ring and six-membered ring **nitroxides** was studied by electron paramagnetic resonance spectrometry, UV-visible spectrophotometry, cyclic voltammetry, and bulk electrolysis. Electron paramagnetic resonance signals from the carbocyclic **nitroxide** derivatives (piperidinyl, pyrrolidinyl, and pyrrolinyl) were unchanged when exposed to enzymatically

generated .O2-, whereas, in the presence of .O2- and reducing agents such as NADH and NADPH, the **nitroxides** underwent reduction to their respective hydroxylamines. The reaction of 4-hydroxy-2,2,6,6-tetramethyl-1-hydroxypiperidine (**Tempol**-H) with .O2- was measured and, in agreement with earlier reports on related compounds, the rate was found to be too slow to be consistent with a mechanism of .O2- dismutation involving the hydroxylamine as an intermediate. Voltammetric analyses of the carbocyclic **nitroxide** derivatives revealed a reversible one-electron redox couple at positive potentials. In contrast, oxazolidine derivatives were irreversibly oxidized. At negative potentials, all of the **nitroxides** studied exhibited a broad, irreversible reductive wave. The rate of .O2- dismutation correlated with the reversible midpoint redox potential. Bulk electrolysis at positive potentials was found to generate a metastable oxidized form of the **nitroxide**. The results indicate that the dismutation of .O2- is catalyzed by the oxoammonium/**nitroxide** redox couple for carbocyclic **nitroxide** derivatives. In addition to the one-electron mitochondrial reduction pathway, the present results suggest the possibility that cellular bioreduction by a two-electron pathway may occur subsequent to oxidation of stable **nitroxides**. Furthermore, the cellular destruction of persistent spin adduct **nitroxides** might also be facilitated by a primary univalent oxidation.

CT Check Tags: Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.
*Ammonium Compounds
***Cyclic N-Oxides**
Electrochemistry: MT, methods
Electron Spin Resonance Spectroscopy: MT, methods
Kinetics
Oxidation-Reduction
Spectrophotometry: MT, methods
Spin Labels
*Superoxides: CH, chemistry
Superoxides: ME, metabolism
Triacetoneamine-N-Oxyl
Xanthine Oxidase: ME, metabolism

RN 11062-77-4 (Superoxides); **2564-83-2 (TEMPO)**; 2896-70-0 (Triacetoneamine-N-Oxyl)

CN EC 1.1.3.22 (Xanthine Oxidase); 0 (Ammonium Compounds); **0 (Cyclic N-Oxides)**; 0 (Spin Labels)

L151 ANSWER 35 OF 58 MEDLINE

AN 92200380 MEDLINE

DN 92200380

TI **Tempol**, a stable free radical, is a novel murine radiation protector.

AU Hahn S M; Tochner Z; **Krishna C M**; Glass J; Wilson L; Samuni A; Sprague M; Venzon D; Glatstein E; **Mitchell J B**; et al

CS Radiation Oncology Branch, National Cancer Institute, NIH, Bethesda, Maryland 20892..

SO CANCER RESEARCH, **(1992 Apr 1)** 52 (7) 1750-3.
Journal code: CNF. ISSN: 0008-5472.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199207

AB **Nitroxide** compounds are stable free radicals which were previously investigated as hypoxic cell radiosensitizers. The stable **nitroxide** 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl (**Tempol**) has recently been shown to protect aerated cells in culture against superoxide generated from hypoxanthine/xanthine oxidase, hydrogen peroxide, and radiation-induced cytotoxicity and to modestly sensitive hypoxic cultured cells. To extend these observations from the cellular level to the whole animal, the toxicity, pharmacology, and in vivo radioprotective effects of **Tempol** were studied in C3H mice. The maximum tolerated dose of **Tempol** administered i.p. was found

to be 275 mg/kg, which resulted in maximal **Tempol** levels in whole blood 5-10 min after injection. Mice were exposed to whole-body radiation in the absence or presence of injected **Tempol** (275 mg/kg) 5-10 min after administration. **Tempol** treatment provided significant radioprotection (P less than 0.0001); the dose of radiation at which 50% of **Tempol**-treated mice die at 30 days was 9.97 Gy, versus 7.84 Gy for control mice. **Tempol** represents a new class of in vivo, non-sulfur-containing radiation protectors. Given the potential for hypoxic radiosensitization and aerobic cell radioprotection, Temporal or other analogues may have potential therapeutic application.

CT Check Tags: Animal; Female; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.

***Cyclic N-Oxides: PD, pharmacology**
Cyclic N-Oxides: PK, pharmacokinetics
Cyclic N-Oxides: TO, toxicity
Dose-Response Relationship, Radiation
Free Radicals
Metabolic Clearance Rate
Mice
Mice, Inbred C3H
***Radiation-Protective Agents: PD, pharmacology**
Time Factors
Whole-Body Irradiation

RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**

CN **0 (Cyclic N-Oxides)**; 0 (Free Radicals); 0 (Radiation-Protective Agents)

L151 ANSWER 36 OF 58 MEDLINE

AN 92198040 MEDLINE

DN 92198040

TI The catecholic metal sequestering agent 1,2-dihydroxybenzene-3,5-disulfonate confers protection against oxidative cell damage.

AU **Krishna C M**; Liebmann J E; Kaufman D; DeGraff W; Hahn S M; McMurry T; **Mitchell J B**; **Russo A**

CS Radiation Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892.

SO ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, **(1992 Apr)** 294 (1) 98-106.
Journal code: 6SK. ISSN: 0003-9861.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199206

AB Tiron (1,2-dihydroxybenzene-3,5-disulfonate), a nontoxic chelator of a variety of metals, is used to alleviate acute metal overload in animals. It is also oxidized to the EPR-detectable semiquinone radical by various biologically relevant oxidants, such as .OH, O2-., alkyl, and alkoxyl radicals. Since Tiron reacts with potentially toxic intracellular species and is also a metal chelator, we evaluated its protective effects in V79 cells subjected to various types of oxidative damage and attempted to distinguish the protection due to direct detoxification of intracellular radicals from that resulting from chelation of redox-active transition metals. We found that Tiron protects Chinese hamster V79 cells against both O2.(-)-induced (and H2O2 via dismutation of O2.-) and H2O2-induced cytotoxicity as measured by clonogenic assays. In experiments where Tiron was incubated with V79 cells and rinsed prior to exposure to HX/XO or H2O2, cytoprotection was observed, indicating that it protects against intracellular oxidative damage. On the other hand, Tiron did not protect V79 cells against the damage caused by ionizing radiation under aerobic conditions, which is predominantly mediated by H., .OH, and hydrated electrons in a metal-independent fashion. We demonstrate also that in in vitro studies, Tiron protects supercoiled DNA from metal-mediated superoxide-dependent strand breaks. We conclude that Tiron is a potentially useful protecting agent against the lethal effects of oxidative stress and suggest that it offers protection by chelating

redox-active transition metal ions, in contrast to earlier reports where the protection by this compound in cellular systems subjected to oxidative damage has been interpreted as due to radical scavenging alone.

CT Check Tags: Animal
*Antioxidants: PD, pharmacology
Cell Line
*Cell Survival: DE, drug effects
Chelating Agents
Cyclic N-Oxides
DNA Damage: DE, drug effects
Electron Spin Resonance Spectroscopy
Free Radical Scavengers
Free Radicals
Hamsters
Hydrogen Peroxide: PD, pharmacology
Iron: ME, metabolism
Oxidation-Reduction
Spin Labels
Superoxides: PD, pharmacology
*Tiron: PD, pharmacology

RN 11062-77-4 (Superoxides); 149-45-1 (Tiron); 3317-61-1 (5,5-dimethyl-1-pyrroline-1-oxide); 7439-89-6 (Iron); 7722-84-1 (Hydrogen Peroxide)

CN 0 (Antioxidants); 0 (Chelating Agents); **0 (Cyclic N-Oxides)**; 0 (Free Radical Scavengers); 0 (Free Radicals); 0 (Spin Labels)

L151 ANSWER 37 OF 58 MEDLINE

AN 92184624 MEDLINE

DN 92184624

TI Topical application of **nitroxide** protects radiation-induced alopecia in guinea pigs.

AU Goffman T; Cuscela D; Glass J; Hahn S; **Krishna C M**; Lupton G; **Mitchell J B**

CS Radiation Oncology Branch, National Cancer Institute, NIH, Bethesda, MD 20892.

SO INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS, **(1992)** 22 (4) 803-6.
Journal code: G97. ISSN: 0360-3016.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199206

AB We have recently found that treatment of Chinese hamster V79 cells with the stable **nitroxide** radical **TEMPOL** (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl) afforded significant protection against superoxide, hydrogen peroxide, and X-ray mediated cytotoxicity. Radiation-induced alopecia is a common radiotherapeutic problem. Topical application of **TEMPOL** was evaluated for possible protective effects against radiation-induced alopecia using guinea pig skin as a model. For single acute X-ray doses up to 30 Gy, **TEMPOL**, when topically applied 15 min prior to irradiation provided a marked increase in the rate and extent of new hair recovery when compared to untreated skin. **TEMPOL** was detected in treated skin specimens with electron paramagnetic resonance (EPR) spectroscopy. Similar measurements of blood samples failed to show any signal resulting from topical application, nor could **TEMPOL** be detected in brain tissue after application on the scalp. **TEMPOL** represents a new class of compounds with potential for selective cutaneous radioprotection without systemic absorption.

CT Check Tags: Animal
Administration, Topical
Alopecia: ET, etiology
*Alopecia: PC, prevention & control
Cyclic N-Oxides: AD, administration & dosage
***Cyclic N-Oxides: TU, therapeutic use**
Guinea Pigs

Radiation Injuries, Experimental: PC, prevention & control
Radiation-Protective Agents: AD, administration & dosage
***Radiation-Protective Agents: TU, therapeutic use**
Skin: RE, radiation effects
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**
CN **0 (Cyclic N-Oxides)**; 0 (Radiation-Protective Agents)

L151 ANSWER 38 OF 58 MEDLINE
AN 92120161 MEDLINE
DN 92120161
TI Antimutagenicity of a low molecular weight superoxide dismutase mimic against oxidative mutagens.
AU DeGraff W G; **Krishna M C; Russo A; Mitchell J B**
CS Radiobiology Section, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892.
SO ENVIRONMENTAL AND MOLECULAR MUTAGENESIS, **(1992)** 19 (1) 21-6.
Journal code: EMM. ISSN: 0893-6692.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199204
AB A set of stable **nitroxide** free radicals that are used as spin labels have been shown to possess metal-independent superoxide dismutase-like activity. Unlike superoxide dismutase (SOD), these compounds are low molecular weight, and readily penetrate into the cell. A representative **nitroxide**, 4-hydroxy-2,2,6,6-tetramethylpiperidinyloxy (**Tempol**), was investigated for antimutagenic activity in the XPRT forward mutation assay in CHO AS52 cells. AS52 cells were exposed to hydrogen peroxide, or the hypoxanthine/xanthine oxidase superoxide generating system, in the presence or absence of 10 mM **Tempol**. **Tempol** itself was not mutagenic or toxic to AS52 cells. **Tempol** protected cells nearly completely from the cytotoxic and mutagenic effects of hydrogen peroxide and hypoxanthine/xanthine oxidase. We have previously shown that **nitroxides** do not alter the extracellular concentration of hydrogen peroxide, and that they are taken up by mammalian cells, suggesting that the antimutagenic activity of **Tempol** is an intracellular phenomenon.
CT Check Tags: Animal
*Antimutagenic Agents
Carcinogenicity Tests
Catalase: PD, pharmacology
***Cyclic N-Oxides: PD, pharmacology**
CHO Cells
Deferoxamine: PD, pharmacology
Hamsters
Hydrogen Peroxide: TO, toxicity
Kinetics
Mutagenicity Tests
Nitrous Oxide: TO, toxicity
Regression Analysis
*Spin Labels
Superoxide Dismutase: PD, pharmacology
Superoxides: TO, toxicity
Xanthine Oxidase: TO, toxicity
RN 10024-97-2 (Nitrous Oxide); 11062-77-4 (Superoxides); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 70-51-9 (Deferoxamine); 7722-84-1 (Hydrogen Peroxide)
CN EC 1.1.3.22 (Xanthine Oxidase); EC 1.11.1.6 (Catalase); **EC 1.15.1.1 (Superoxide Dismutase)**; 0 (Antimutagenic Agents); **0 (Cyclic N-Oxides)**; 0 (Spin Labels)

L151 ANSWER 39 OF 58 MEDLINE
AN 92112732 MEDLINE

DN 92112732
TI Identification and characterization of the enzymatic activity of zeta-crystallin from guinea pig lens. A novel NADPH:quinone oxidoreductase.
AU Rao P V; **Krishna C M**; Zigler J S Jr
CS Laboratory of Mechanisms of Ocular Diseases, National Eye Institute, National Institutes of Health, Bethesda, Maryland 20892.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, **(1992 Jan 5)** 267 (1) 96-102.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199204
AB zeta-Crystallin is a major protein in the lens of certain mammals. In guinea pigs it comprises 10% of the total lens protein, and it has been shown that a mutation in the zeta-crystallin gene is associated with autosomal dominant congenital cataract. As with several other lens crystallins of limited phylogenetic distribution, zeta-crystallin has been characterized as an "enzyme/crystallin" based on its ability to reduce catalytically the electron acceptor 2,6-dichlorophenolindophenol. We report here that certain naturally occurring quinones are good substrates for the enzymatic activity of zeta-crystallin. Among the various quinones tested, the orthoquinones 1,2-naphthoquinone and 9,10-phenanthrenequinone were the best substrates whereas menadione, ubiquinone, 9,10-anthraquinone, vitamins K1 and K2 were inactive as substrates. This quinone reductase activity was NADPH specific and exhibited typical Michaelis-Menten kinetics. Activity was sensitive to heat and sulfhydryl reagents but was very stable on freezing. Dicumarol (Ki = 1.3 x 10(-5) M) and nitrofurantoin (Ki = 1.4 x 10(-5) M) inhibited the activity competitively with respect to the electron acceptor, quinone. NADPH protected the enzyme against inactivation caused by heat, N-ethylmaleimide, or H2O2. Electron paramagnetic resonance spectroscopy of the reaction products showed formation of a semiquinone radical. The enzyme activity was associated with O2 consumption, generation of O2- and H2O2, and reduction of ferricytochrome c. These properties indicate that the enzyme acts through a one-electron transfer process. The substrate specificity, reaction characteristics, and physicochemical properties of zeta-crystallin demonstrate that it is an active NADPH:quinone oxidoreductase distinct from quinone reductases described previously.
CT Check Tags: Animal; Support, Non-U.S. Gov't
Catalysis
Crystallins: IP, isolation & purification
*Crystallins: ME, metabolism
Cyclic N-Oxides: ME, metabolism
Cytochrome c: ME, metabolism
Dicumarol: PD, pharmacology
Electron Spin Resonance Spectroscopy
Guinea Pigs
Hydrogen Peroxide: ME, metabolism
Kinetics
Lens, Crystalline: DE, drug effects
Lens, Crystalline: EN, enzymology
*Lens, Crystalline: ME, metabolism
Naphthoquinones: ME, metabolism
Nitrofurantoin: PD, pharmacology
*NADP: ME, metabolism
Oxygen: ME, metabolism
Quinone Reductases: AI, antagonists & inhibitors
*Quinone Reductases: ME, metabolism
Quinones: ME, metabolism
Spin Labels
Substrate Specificity
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 481-39-0 (juglone); 53-59-8 (NADP); 66-76-2 (Dicumarol); 67-20-9 (Nitrofurantoin); 7722-84-1 (Hydrogen Peroxide); 7782-44-7 (Oxygen); 9007-43-6 (Cytochrome

c)
CN EC 1.6.99. (Quinone Reductases); 0 (Crystallins); **0 (Cyclic N-Oxides)**; 0 (Naphthoquinones); 0 (Quinones); 0 (Spin Labels)

L151 ANSWER 40 OF 58 MEDLINE
AN 92076395 MEDLINE
DN 92076395
TI Mechanisms of hypoxic and aerobic cytotoxicity of mitomycin C in Chinese hamster V79 cells.
AU **Krishna M C**; DeGraff W; Tamura S; Gonzalez F J; Samuni A; **Russo A**; **Mitchell J B**
CS Radiation Oncology Branch, National Cancer Institute, NIH, Bethesda, Maryland 20892.
SO CANCER RESEARCH, **(1991 Dec 15)** 51 (24) 6622-8.
Journal code: CNF. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199203
AB Mitomycin C (MMC) induced aerobic and hypoxic cytotoxicity in Chinese hamster V79 cells was studied to evaluate the role of the 1-electron versus 2-electron reductive bioactivation. Superoxide dismutase, catalase, and desferal had no protective effects on the aerobic or hypoxic cytotoxicity of MMC, whereas **Tempol** and **Tempol**-H, which are known to interrupt and terminate radical reactions, provided partial protection under aerobic conditions. However, under hypoxic conditions, **Tempol** provided complete protection whereas **Tempol**-H was ineffective. Electron paramagnetic resonance and spin-trapping investigations, designed to study the mechanisms of such protective effects, confirmed that MMC is activated by the human NADPH:cytochrome P-450 oxidoreductase to its semiquinone radical and that, under aerobic conditions, the semiquinone radical reduces molecular oxygen. Under hypoxic conditions, the semiquinone of MMC reduces H2O2 to produce OH radicals as detected by electron paramagnetic resonance-spin trapping with 5,5-dimethyl-1-pyrroline N-oxide. The 1-electron reduced product of MMC was also found to reduce **Tempol** to the hydroxylamine, **Tempol**-H, whereas oxidation of **Tempol**-H by MMC-. was negligible. Cell survival studies and electron paramagnetic resonance observations indicate that the hypoxic cytotoxicity of MMC is mediated by 1-electron activation to its semiquinone intermediate. Under aerobic conditions, the steady state concentration of this intermediate is low due to the facile autooxidation of the semiquinone producing O2-. and H2O2 which are capable of causing oxidative cytotoxicity. **Tempol**, which can accept an electron from reducing radical species, completely inhibited the hypoxic cytotoxicity of MMC indicating MMC-., the semiquinone of MMC as the species responsible for DNA alkylation and selective hypoxic cytotoxicity of MMC. Our results also indicate that the aerobic cytotoxicity is mediated by other processes in addition to the 1-electron mediated activation.
CT Check Tags: Animal; In Vitro; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.
Aerobiosis
Alkylating Agents: CH, chemistry
Anoxia
Cell Line
Cell Survival: DE, drug effects
Cyclic N-Oxides: CH, chemistry
***Cyclic N-Oxides: PD, pharmacology**
Electron Spin Resonance Spectroscopy
Free Radicals
Hamsters
Hydrogen Peroxide: CH, chemistry
*Mitomycin: TO, toxicity
Oxidation-Reduction
Superoxide Dismutase: ME, metabolism

RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 50-07-7 (Mitomycin); 7722-84-1 (Hydrogen Peroxide)
CN **EC 1.15.1.1 (Superoxide Dismutase)**; 0 (Alkylating Agents); **0 (Cyclic N-Oxides)**; 0 (Free Radicals)

L151 ANSWER 41 OF 58 MEDLINE
AN 91378540 MEDLINE
DN 91378540
TI Inhibition of oxygen-dependent radiation-induced damage by the **nitroxide** superoxide dismutase mimic, **tempol**.
AU **Mitchell J B**; DeGraff W; Kaufman D; **Krishna M C**; Samuni A; Finkelstein E; Ahn M S; Hahn S M; Gamson J; **Russo A**
CS Radiobiology Section, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892..
SO ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, **(1991 Aug 15)** 289 (1) 62-70.
Journal code: 6SK. ISSN: 0003-9861.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199112
AB Stable **nitroxide** radicals have been previously shown to function as superoxide dismutase (SOD)2 mimics and to protect mammalian cells against superoxide and hydrogen peroxide-mediated oxidative stress. These unique characteristics suggested that **nitroxides**, such as 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (**Tempol**), might protect mammalian cells against ionizing radiation. Treating Chinese hamster cells under aerobic conditions with 5, 10, 50, and 100 mM **Tempol** 10 min prior to X-rays resulted in radiation protection factors of 1.25, 1.30, 2.1, and 2.5, respectively. However, the reduced form of **Tempol** afforded no protection. **Tempol** treatment under hypoxic conditions did not provide radioprotection. Aerobic X-ray protection by **Tempol** could not be attributed to the induction of intracellular hypoxia, increase in intracellular glutathione, or induction of intracellular SOD mRNA. **Tempol** thus represents a new class of non-thiol-containing radiation protectors, which may be useful in elucidating the mechanism(s) of radiation-induced cellular damage and may have broad applications in protecting against oxidative stress.
CT Check Tags: Animal
Blotting, Northern
Cell Line
Cell Membrane: ME, metabolism
Cell Survival: DE, drug effects
*Cell Survival: RE, radiation effects
Cyclic N-Oxides: ME, metabolism
***Cyclic N-Oxides: PD, pharmacology**
Electron Spin Resonance Spectroscopy
Gene Expression: DE, drug effects
Glutathione: ME, metabolism
Hamsters
Oxygen: ME, metabolism
*Oxygen: PD, pharmacology
*Radiation-Protective Agents: PD, pharmacology
RNA, Messenger: ME, metabolism
Spin Labels
Superoxide Dismutase: GE, genetics
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 70-18-8 (Glutathione); 7782-44-7 (Oxygen)
CN EC 1.15.1.1 (Superoxide Dismutase); **0 (Cyclic N-Oxides)**; 0 (Radiation-Protective Agents); 0 (RNA, Messenger); 0 (Spin Labels)

L151 ANSWER 42 OF 58 MEDLINE
AN 91301504 MEDLINE
DN 91301504

TI Superoxide production by stimulated neutrophils: temperature effect.
AU Black C D; Cook J A; **Russo A**; Samuni A
CS Radiation Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892..
SO FREE RADICAL RESEARCH COMMUNICATIONS, **(1991)** 12-13 Pt 1 27-37. Journal code: FRR. ISSN: 8755-0199.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199110
AB Activation of neutrophils results in a one-electron reduction of oxygen to produce the superoxide anion and other oxygen-derived, microbicidal species. Evidence from many kinetic studies of oxygen-derived radicals generated by stimulated neutrophils in vitro shows that radical production is optimal at 37 degrees C but only lasts several minutes and then rapidly subsides. These findings support the widely held perception that the neutrophil's "oxidative burst" is a transitory event that peaks within minutes of stimulation and ends shortly thereafter. However, while some studies have shown that under controlled conditions stimulated neutrophils can generate superoxide continuously for several hours, others have observed that the superoxide formation by neutrophils stimulated in buffer at 37 degrees C does not persist. To reconcile the conflicting findings and to better understand neutrophil function, we have reinvestigated the effect of temperature on the kinetics of radical generation by PMA-stimulated cells. Electron paramagnetic resonance spectroscopy coupled with spin-trapping and SOD-inhibitable ferricytochrome c reduction were used to monitor superoxide production by neutrophils stimulated at either 25 degrees C or 37 degrees C in RPMI 1640 medium or in Hank's balanced salt solution. When oxygen was supplied continuously, neutrophils stimulated at 25 degrees C in buffer or in medium generated superoxide for several hours but at 37 degrees C, particularly in HBSS, O2- formation strikingly and rapidly decreased. This cessation of superoxide generation was reversible by lowering the temperature back to 25 degrees C. These data imply that in vivo neutrophils may be capable of generating oxy-radicals for prolonged periods. In part, our results may also explain the often observed termination of neutrophil-derived radical formation in vitro and help to dispel the perception that neutrophil-derived oxy-radical production is an ephemeral phenomenon.
CT Check Tags: Human
Cyclic N-Oxides: AN, analysis
Cytochrome c: ME, metabolism
Electron Spin Resonance Spectroscopy
Free Radicals
Neutrophils: DE, drug effects
*Neutrophils: ME, metabolism
Oxidation-Reduction
Oxygen: ME, metabolism
Peroxidase: ME, metabolism
Spin Labels
Superoxide Dismutase: ME, metabolism
*Superoxides: ME, metabolism
Temperature
Tetradecanoylphorbol Acetate: PD, pharmacology
Time Factors
RN 11062-77-4 (Superoxides); 16561-29-8 (Tetradecanoylphorbol Acetate); 3317-61-1 (5,5-dimethyl-1-pyrroline-1-oxide); 7782-44-7 (Oxygen); 85963-89-9 (5,5-dimethyl-5-hydroperoxy-1-pyrrolidinyloxy); 9007-43-6 (Cytochrome c)
CN EC 1.11.1.7 (Peroxidase); **EC 1.15.1.1 (Superoxide Dismutase)**; **0 (Cyclic N-Oxides)**; 0 (Free Radicals); 0 (Spin Labels)

L151 ANSWER 43 OF 58 MEDLINE
AN 91301493 MEDLINE
DN 91301493
TI **Nitroxide** SOD-mimics: modes of action.

AU Samuni A; **Mitchell J B**; DeGraff W; **Krishna C M**; Samuni U; **Russo A**
CS Radiation Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.
SO FREE RADICAL RESEARCH COMMUNICATIONS, **(1991)** 12-13 Pt 1 187-94. Journal code: FRR. ISSN: 8755-0199.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199110
AB Low molecular weight superoxide dismutase mimics have been shown to afford protection from oxidative damage. Such SOD-mimics can readily permeate cell membrane achieving sufficiently high levels both inside and outside the cell to effectively detoxify intracellular O2-.. Preliminary findings also indicated that metal-based and metal-free SOD-mimics can protect hypoxic cells from H2O2-induced damage. The present study explored the possibility that SOD-mimics such as desferrioxamine-Mn(III) chelate [DF-Mn] or cyclic **nitroxide** stable free radicals could protect from O2-.-independent damage. Killing of monolayered V79 Chinese hamster cells was induced by H2O2 or by t-butyl hydroperoxide (t-BHP) and assayed clonogenically. Neither catalase nor native SOD protected the cells from t-BHP. In contrast, both DF-Mn and cyclic **nitroxides** protected suggesting cytotoxic processes independent of O2-. or of O2-.-derived active species. The inhibition of the damage by both metal-free and metal-based SOD mimics is attributable to either SOD-mimic reacting with reduced transition metal to block the Fenton reaction and/or intercepting and detoxifying intracellular organic free radicals.
CT Check Tags: Animal; Comparative Study
*Antioxidants: PD, pharmacology
Catalase: PD, pharmacology
Cell Line
Cricetulus
***Cyclic N-Oxides: PD, pharmacology**
Cytochrome c: ME, metabolism
*Deferoxamine: PD, pharmacology
Fibroblasts: DE, drug effects
*Free Radical Scavengers
Free Radicals
Hamsters
Hydrogen Peroxide: AI, antagonists & inhibitors
Hydrogen Peroxide: PD, pharmacology
Lung
Models, Chemical
Organometallic Compounds: PD, pharmacology
Oxidation-Reduction
Peroxides: AI, antagonists & inhibitors
Peroxides: PD, pharmacology
***Superoxide Dismutase: PD, pharmacology**
*Superoxides: ME, metabolism
RN 11062-77-4 (Superoxides); 125892-49-1 (manganese desferioxamine); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 70-51-9 (Deferoxamine); 75-91-2 (tert-Butylhydroperoxide); 7722-84-1 (Hydrogen Peroxide); 9007-43-6 (Cytochrome c)
CN EC 1.11.1.6 (Catalase); **EC 1.15.1.1 (Superoxide Dismutase)**; 0 (Antioxidants); **0 (Cyclic N-Oxides)**; 0 (Free Radical Scavengers); 0 (Free Radicals); 0 (Organometallic Compounds); 0 (Peroxides)

L151 ANSWER 44 OF 58 MEDLINE
AN 91245792 MEDLINE
DN 91245792
TI Spin trap protection from tumor necrosis factor cytotoxicity.
AU Pogrebniak H; Matthews W; **Mitchell J**; **Russo A**; Samuni A; Pass H
CS Thoracic Oncology Section, National Cancer Institute, National Institutes

of Health, Bethesda, Maryland 20892.
SO JOURNAL OF SURGICAL RESEARCH, **(1991 May)** 50 (5) 469-74.
Journal code: K7B. ISSN: 0022-4804.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199109
AB Tumor necrosis factor (TNF) facilitates superoxide production, and spin traps may detoxify superoxide by acting as superoxide dismutase mimics. We investigated the ability of a stable **nitroxide** spin trap, **TEMPOL**, to protect TNF-sensitive cells from exogenously added TNF. WEHI or L929 cells were incubated with TNF (500 units/ml) for 18 hr either simultaneously with 0 to 8 mM **TEMPOL** or with the **TEMPOL** added at varying intervals after TNF exposure. A dose-dependent increase in survival was noted in the **TEMPOL**-treated cells, with 92 +/- 2% survival of WEHIs treated with 4 mM **TEMPOL** compared to 26 +/- 1% survival for non-**TEMPOL**-exposed cells (P2 less than 0.01). Significant increases in survival could be accomplished with as late as 15-hr delayed addition of the compound. The mechanism of protection does not seem to involve newly synthesized protein, and Northern blot analysis revealed that **TEMPOL** does not induce the genes for MnSOD or Cu-ZnSOD. The ability of **TEMPOL** to protect against TNF injury, even when exposure is delayed, may prove useful in conditions thought to be associated with free radical-lymphokine interactions such as ischemia-reperfusion, oxygen toxicity, or sepsis.
CT Check Tags: Animal
Blotting, Northern
Cell Line
***Cyclic N-Oxides: PD, pharmacology**
Cycloheximide: PD, pharmacology
*Cytotoxins: AI, antagonists & inhibitors
Dose-Response Relationship, Drug
Kinetics
*Spin Labels
Time Factors
Tumor Cells, Cultured
*Tumor Necrosis Factor: AI, antagonists & inhibitors
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 66-81-9 (Cycloheximide)
CN **0 (Cyclic N-Oxides)**; 0 (Cytotoxins); 0 (Spin Labels); 0 (Tumor Necrosis Factor)

L151 ANSWER 45 OF 58 MEDLINE
AN 91217223 MEDLINE
DN 91217223
TI **Nitroxide** stable radicals protect beating cardiomyocytes against oxidative damage.
AU Samuni A; Winkelsberg D; Pinson A; Hahn S M; **Mitchell J B**; **Russo A**
CS Department of Molecular Biology, School of Medicine, Hebrew University, Jerusalem, Israel..
SO JOURNAL OF CLINICAL INVESTIGATION, **(1991 May)** 87 (5) 1526-30.
Journal code: HS7. ISSN: 0021-9738.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199108
AB The protective effect of stable **nitroxide** radicals against oxidative damage was studied using cardiomyocyte cultures obtained from newborn rats. Monolayered cardiomyocytes were exposed to H2O2 and the effect on spontaneous beating and leakage of LDH was determined. Hydrogen peroxide irreversibly blocked rhythmic beating and resulted in a significant membrane injury as shown by release of LDH. The injury was prevented by catalase which removes H2O2 and by cell-permeable,

metal-chelating agents such as desferrioxamine or bipyridine. In contrast, reagents which are excluded from the cell such as superoxide dismutase or DTPA did not protect the cells against H2O2. Five- and six-membered ring, stable **nitroxide** radicals which have previously been shown to chemically act as low-molecular weight, membrane-permeable, SOD-mimetic compounds provided full protection. The **nitroxides** prevented leakage of LDH and preserved normal cardiomyocyte contractility, presumably by intercepting intracellular O2-radicals. Alternatively, protection may result through **nitroxides** reacting with reduced transition metal ions or by detoxifying secondary organic radicals.

CT Check Tags: Animal
Cells, Cultured
Deferoxamine: PD, pharmacology
Heart: DE, drug effects
*Hydrogen Peroxide: TO, toxicity
Hydroxides
Lactate Dehydrogenase: SE, secretion
*Myocardium: ME, metabolism
***Nitrogen Oxides: PD, pharmacology**
Oxidation-Reduction
Rats

RN 3352-57-6 (Hydroxyl Radical); 70-51-9 (Deferoxamine); 7722-84-1 (Hydrogen Peroxide)

CN EC 1.1.1.27 (Lactate Dehydrogenase); 0 (Hydroxides); **0 (Nitrogen Oxides)**

L151 ANSWER 46 OF 58 MEDLINE

AN 91105139 MEDLINE

DN 91105139

TI **Nitroxides** block DNA scission and protect cells from oxidative damage.

AU Samuni A; Godinger D; Aronovitch J; **Russo A; Mitchell J B**

CS Molecular Biology, School of Medicine, Hebrew University, Jerusalem, Israel.

SO BIOCHEMISTRY, **(1991 Jan 15)** 30 (2) 555-61.
Journal code: A0G. ISSN: 0006-2960.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199105

AB The protective effect of cyclic stable **nitroxide** free radicals, having SOD-like activity, against oxidative damage was studied by using Escherichia coli xthA DNA repair-deficient mutant hypersensitive to H2O2. Oxidative damage induced by H2O2 was assayed by monitoring cell survival. The metal chelator 1,10-phenanthroline (OP), which readily intercalates into DNA, potentiated the H2O2-induced damage. The extent of in vivo DNA scission and degradation was studied and compared with the loss of cell viability. The extent of DNA breakage correlated with cell killing, supporting previous suggestions that DNA is the crucial cellular target of H2O2 cytotoxicity. The xthA cells were protected by catalase but not by superoxide dismutase (SOD). Both five- and six-membered ring **nitroxides**, having SOD-like activity, protected growing and resting cells from H2O2 toxicity, without lowering H2O2 concentration. To check whether **nitroxides** protect against O2.(-)-independent injury also, experiments were repeated under hypoxia. These **nitroxides** also protected hypoxic cells against H2O2, suggesting alternative modes of protection. Since **nitroxides** were found to reoxidize DNA-bound iron(II), the present results suggest that **nitroxides** protect by oxidizing reduced transition metals, thus interfering with the Fenton reaction.

CT Check Tags: In Vitro
Cell Survival: DE, drug effects
*DNA: CH, chemistry
*DNA Damage

Escherichia coli: DE, drug effects
Ferrous Compounds: CH, chemistry
Free Radicals
Hydrogen Peroxide: CH, chemistry
***Nitrogen Oxides: CH, chemistry**
Nitrogen Oxides: PD, pharmacology
Oxidation-Reduction
Phenanthrolines: PD, pharmacology
Solubility
Superoxides: CH, chemistry
RN 11062-77-4 (Superoxides); 66-71-7 (1,10-phenanthroline); 7722-84-1 (Hydrogen Peroxide); 9007-49-2 (DNA)
CN 0 (Ferrous Compounds); 0 (Free Radicals); **0 (Nitrogen Oxides)**; 0 (Phenanthrolines)

L151 ANSWER 47 OF 58 MEDLINE
AN 90353766 MEDLINE
DN 90353766
TI Superoxide reaction with **nitroxides**.
AU Samuni A; **Krishna C M; Mitchell J B**; Collins C R; **Russo A**
CS Molecular Biology, Hebrew University Medical School, Jerusalem, Israel..
SO FREE RADICAL RESEARCH COMMUNICATIONS, **(1990)** 9 (3-6) 241-9.
Journal code: FRR. ISSN: 8755-0199.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199011
AB Stable, free radical **nitroxides** are commonly used ESR spectroscopy tools. However, it has recently been found that ESR observable signal from 5-membered ring spin-adducts or stable label **nitroxides** is lost or diminished by reaction with superoxide. A similar radical-radical annihilation was not found for six membered ring **nitroxide** radicals. To discern why six-membered ring **nitroxides** are not reduced under superoxide flux generated by hypoxanthine/xanthine oxidase, spectrophoptmetric (Cyt CIII) and chemiluminescence (lucigenin) and ESR assays were used to follow the reactions. Spectrophotometry and chemiluminescence clearly demonstrated that the six-membered piperidine-1-oxyl compounds (**TEMPO**, **TEMPOL**, and TEMPAMIN) rapidly react with superoxide: rate constants at pH 7.8 ranging from 7 x 10(4) to 1.2 x 10(5) M-1 s-1. The absence of detectable ESR signal loss results from facile re-oxidation of the corresponding hydroxylamine by superoxide. To fully corroborate the efficiency of the 6-membered **nitroxide** superoxide dismutase activity, they were shown to protect fully mammalian cells from oxidative damage resulting from exposure to the superoxide and hydrogen peroxide generating system hypoxanthine/xanthine oxidase. Since six-membered cyclic **nitroxides** react with superoxide about 2 orders of magnitude faster than the corresponding 5-membered ring **nitroxides**, they may ultimately be more useful as superoxide oxide dismutase mimetic agents.
CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.
Cell Line
Cell Survival: DE, drug effects
Cyclic N-Oxides: CS, chemical synthesis
Electron Spin Resonance Spectroscopy
*Free Radicals
***Nitrogen Oxides**
Nitrogen Oxides: ME, metabolism
Nitrogen Oxides: PD, pharmacology
Oxazoles: CS, chemical synthesis
Reproducibility of Results
Spiro Compounds: CS, chemical synthesis
*Superoxides

Superoxides: AI, antagonists & inhibitors
Superoxides: ME, metabolism
RN 11062-77-4 (Superoxides); 133906-30-6 (2-spirocyclohexane doxyl (2-spirocyclohexane-5,5-dimethyl-3-oxazolidinoxyl)); 65162-38-1 (2-ethyl-2,5,5-trimethyl-3-oxazolidinoxyl)
CN **0 (Cyclic N-Oxides)**; 0 (Free Radicals); **0 (Nitrogen Oxides)**; 0 (Oxazoles); 0 (Spiro Compounds)

L151 ANSWER 48 OF 58 MEDLINE
AN 90268031 MEDLINE
DN 90268031
TI Biologically active metal-independent superoxide dismutase mimics.
AU **Mitchell J B**; Samuni A; **Krishna M C**; DeGraff W G; Ahn M S; Samuni U; **Russo A**
CS Radiation Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892..
SO BIOCHEMISTRY, **(1990 Mar 20)** 29 (11) 2802-7.
Journal code: A0G. ISSN: 0006-2960.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199009
AB Superoxide dismutase (SOD) is an enzyme that detoxifies superoxide (O2.-), a potentially toxic oxygen-derived species. Attempts to increase intracellular concentrations of SOD by direct application are complicated because SOD, being a relatively large molecule, does not readily cross cell membranes. We have identified a set of stable **nitroxides** that possess SOD-like activity, have the advantage of being low molecular weight, membrane permeable, and metal independent, and at pH 7.0 have reaction rate constants with O2.- ranging from 1.1 x 10(3) to 1.3 x 10(6) M-1 s-1. These SOD mimics protect mammalian cells from damage induced by hypoxanthine/xanthine oxidase and H2O2, although they exhibit no catalase-like activity. In addition, the **nitroxide** SOD mimics rapidly oxidize DNA-FeII and thus may interrupt the Fenton reaction and prevent formation of deleterious OH radicals and/or higher oxidation states of metal ions. Whether by SOD-like activity and/or interception of an electron from redox-active metal ions they protect cells from oxidative stress and may have use in basic and applied biological studies.
CT Check Tags: Animal
Cells, Cultured
Chemistry
Cytochrome c: ME, metabolism
DNA: ME, metabolism
Electron Spin Resonance Spectroscopy
Ferrous Compounds: ME, metabolism
Hamsters
Nitrogen Oxides: ME, metabolism
Oxazoles
Oxidation-Reduction
***Superoxide Dismutase**
Superoxide Dismutase: GE, genetics
RN 504-76-7 (oxazolidine); 9007-43-6 (Cytochrome c); 9007-49-2 (DNA)
CN **EC 1.15.1.1 (Superoxide Dismutase)**; 0 (Ferrous Compounds); **0 (Nitrogen Oxides)**; 0 (Oxazoles)

L151 ANSWER 49 OF 58 MEDLINE
AN 90105392 MEDLINE
DN 90105392
TI Free radicals induced by adriamycin-sensitive and adriamycin-resistant cells: a spin-trapping study.
AU Alegria A E; Samuni A; **Mitchell J B**; Riesz P; **Russo A**
CS Radiation Oncology Branch, National Cancer Institute, Bethesda, Maryland 20892.
NC 3-734-GM 12247 (NIGMS)
SO BIOCHEMISTRY, **(1989 Oct 17)** 28 (21) 8653-8.

Journal code: A0G. ISSN: 0006-2960.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199004
AB The radicals generated by adriamycin-sensitive (CHO-AB) and adriamycin-resistant (CHO-C5) Chinese hamster ovary cells as well as by adriamycin-sensitive and -resistant human breast cancer cells (MCF7-WT and MCF7-ADR) have been studied with spin-trapping and ESR spectroscopy. During anoxic exposure to adriamycin (ADR) both pairs of cell lines produced the broad ESR singlet characteristic of ADR semiquinone (AQ.). By use of tris(oxalato)chromate (CrOx) as an extracellular line-broadening agent, the distribution of AQ. between the intra- and extracellular compartments was studied. For cell densities of (1-3) X 10(7) cells/mL, CrOx eliminated most, though not all, of the ESR signal, indicating that the AQ. radicals freely diffuse and partition between the intra- and extracellular compartments proportionally to their respective volumes. Similar behavior was exhibited by all four cell lines studied. Upon introduction of oxygen to anoxic cells in the presence of the spin trap 5,5-dimethylpyrroline N-oxide (DMPO), the AQ. signal was replaced by that of the DMPO-OH spin adduct. Metal chelators such as desferrioxamine had no effect on DMPO-OH or AQ. formation. Superoxide dismutase, not catalase, totally eliminated the ESR signal, indicating that DMPO-OH produced by ADR-treated cells originates from superoxide rather than from .OH produced from H2O2. In the presence of CrOx, the DMPO-OH signal was not distinguishable from the background noise, thus excluding any contribution to the signal by intracellular spin adducts.(ABSTRACT TRUNCATED AT 250 WORDS)
CT Check Tags: Animal; Female; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Breast Neoplasms
Cell Line
Cell Survival
Chromates: PD, pharmacology
Cricetulus
Cyclic N-Oxides
*Doxorubicin: AA, analogs & derivatives
Doxorubicin: ME, metabolism
*Doxorubicin: PD, pharmacology
Drug Resistance
Electron Spin Resonance Spectroscopy
Free Radicals
Hamsters
Hydroxides: ME, metabolism
Oxalates: PD, pharmacology
*Superoxides: ME, metabolism
Tumor Cells, Cultured
RN 11062-77-4 (Superoxides); 14217-01-7 (tris(oxalato)chromate(III)); 23214-92-8 (Doxorubicin); 3317-61-1 (5,5-dimethyl-1-pyrroline-1-oxide); 3352-57-6 (Hydroxyl Radical)
CN 0 (adriamycin semiquinone radicals); 0 (Chromates); **0 (Cyclic N-Oxides)**; 0 (Free Radicals); 0 (Hydroxides); 0 (Oxalates)

L151 ANSWER 50 OF 58 MEDLINE
AN 90002334 MEDLINE
DN 90002334
TI The in vitro screening of methylated 4-oxypiperidine compounds for inhibition of protein synthesis in a rabbit reticulocyte cell-free translation system.
AU Kuznetsov D A; Zavijalov N V; Kelman G J; Govorkov A V
CS Laboratory of Toxicology, Moscow City Station for Sanitation and Epidemiology, USSR..
SO CELL BIOLOGY AND TOXICOLOGY, **(1986 Sep)** 2 (3) 337-40.
Journal code: CBT. ISSN: 0742-2091.
CY United States

DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199001
AB A variety of methylated 4-oxypiperidine derivatives were tested for their ability to inhibit protein synthesis in vitro. A direct correlation was found between the extent of methylation of these compounds and their inhibitory activity in a rabbit reticulocyte lysate cell-free translation system.
CT Check Tags: Animal; In Vitro
***Cyclic N-Oxides: PD, pharmacology**
Methylation
*Protein Synthesis Inhibitors: PD, pharmacology
*Proteins: BI, biosynthesis
Rabbits
***Translation, Genetic: DE, drug effects**
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**
CN **0 (Cyclic N-Oxides)**; 0 (Protein Synthesis Inhibitors)

L151 ANSWER 51 OF 58 MEDLINE
AN 89255168 MEDLINE
DN 89255168
TI Localization of the active center of **nitroxide** radical reduction in rat liver microsomes: its relation to cytochrome P-450 and membrane fluidity.
AU Utsumi H; Shimakura A; Kashiwagi M; Hamada A
CS Department of Health Chemistry, School of Pharmaceutical Sciences, Showa University, Tokyo..
SO JOURNAL OF BIOCHEMISTRY, **(1989 Feb)** 105 (2) 239-44.
Journal code: HIF. ISSN: 0021-924X.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198909
AB The properties and localization of the active center of NADPH-dependent **nitroxide** radical reduction in rat liver microsomes were investigated with the following five spin-probes as substrates; tetramethylpiperidinol-N-oxyl (**TEMPOL**) and four spin-labeled stearic acid derivatives with a **nitroxide** radical at the 5th, 7th, 12th, or 16th position of the hydrocarbon chain (abbreviated as 5SLS, 7SLS, 12SLS, and 16SLS, respectively). The ESR signals of these spin-probes in microsomes decreased on the addition of NADPH, and the decay was inhibited by pretreatment with SKF-525A. Experiments with various microsomal preparations induced by phenobarbital (PB), polychlorinated biphenyls (PCB), or 3-methylcholanthrene (3-MC) revealed that the reduction rate was correlated to the concentration of cytochrome P-450 but not to that of NADPH reductase. Thus, the **nitroxide** radicals of the SLSs and **TEMPOL** seem to be reduced by the combined action of NADPH-cytochrome P-450 reductase and cytochrome P-450. The decay showed a lag time, but no distinct correlation was observed between the lag time and the spin-probe species. On the other hand, the initial velocity of the **nitroxide** reduction depended strongly on the spin-probe species. Among the five spin-probes, 7SLS was reduced most quickly, followed by 5SLS, 12SLS, **TEMPOL**, and 16SLS in that order. The reduction rate varied from 0.18/min for 7SLS to 0.08/min for 16SLS. There was a linear relation between the cytochrome P-450 content and the reduction rate.(ABSTRACT TRUNCATED AT 250 WORDS)
CT Check Tags: Animal; In Vitro; Male; Support, Non-U.S. Gov't
Cytochrome P-450: BI, biosynthesis
*Cytochrome P-450: ME, metabolism
Electron Spin Resonance Spectroscopy
Enzyme Induction: DE, drug effects
Membrane Fluidity
Methylcholanthrene: PD, pharmacology
*Microsomes, Liver: EN, enzymology

***Nitrogen Oxides: ME, metabolism**
Oxidation-Reduction
Phenobarbital: PD, pharmacology
Polychlorinated Biphenyls: PD, pharmacology
Rats
Rats, Inbred Strains
RN 14332-28-6 (nitroxyl); 50-06-6 (Phenobarbital); 56-49-5 (Methylcholanthrene); 9035-51-2 (Cytochrome P-450)
CN **0 (Nitrogen Oxides)**; 0 (Polychlorinated Biphenyls)

L151 ANSWER 52 OF 58 MEDLINE
AN 89212110 MEDLINE
DN 89212110
TI Superoxide reaction with **nitroxide** spin-adducts.
AU Samuni A; **Krishna C M**; Riesz P; Finkelstein E; **Russo A**
CS Department of Molecular Biology, School of Medicine, Hebrew University of Jerusalem, Israel.
SO FREE RADICAL BIOLOGY AND MEDICINE, **(1989)** 6 (2) 141-8.
Journal code: FRE. ISSN: 0891-5849.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198908
AB The reactions of superoxide radical with persistent **nitroxide** spin-adducts or with stable spin-labels were studied using ESR spectrometry. Superoxide radicals were produced enzymatically using xanthine - xanthine oxidase or chemically by dissolving potassium superoxide in DMSO. Hydroxyl and methyl spin-adducts of the spin-trap DMPO were performed by sonolysis and subsequently reacted with superoxide radical. Superoxide-induced depletion of DMPO--OH obeyed second order kinetics. Contrary to previously published mechanisms, the reaction requires neither transition metal ions nor thiols. The depleted spin-adducts could not be restored by reoxidation with ferricyanide or copper +H2O2; thus, the superoxide-mediated destruction does not result in a mere one-electron reduction product. Superoxide also depletes other DMPO spin-adducts including DMPO--CH3 and DMPO--H, but not PBN--CH3. In addition, some 5-membered ring stable **nitroxides** are depleted by superoxide in a pseudo-zero order reaction. In studying systems which generate O2- and OH, the superoxide-induced destruction of DMPO--OH may well lead to erroneous conclusions regarding the primary radicals produced. In particular this reaction might be operative under circumstances where elevated rates of superoxide production take place, such as during oxygen consumption "burst" in phagocytosis, degranulation, or paraquat intoxication.
CT Check Tags: Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.
***Cyclic N-Oxides**
Electron Spin Resonance Spectroscopy
Free Radicals
Hydrogen Peroxide: PD, pharmacology
Kinetics
Oxidation-Reduction
Spin Labels
*Superoxides
Superoxides: ME, metabolism
Xanthine Oxidase: ME, metabolism
Xanthines: ME, metabolism
RN 11062-77-4 (Superoxides); 3317-61-1 (5,5-dimethyl-1-pyrroline-1-oxide); 69-89-6 (Xanthine); 7722-84-1 (Hydrogen Peroxide)
CN EC 1.1.3.22 (Xanthine Oxidase); **0 (Cyclic N-Oxides)**; 0 (Free Radicals); 0 (Spin Labels); 0 (Xanthines)

L151 ANSWER 53 OF 58 MEDLINE
AN 89053953 MEDLINE
DN 89053953
TI A novel metal-free low molecular weight superoxide dismutase mimic.

AU Samuni A; **Krishna C M**; Riesz P; Finkelstein E; **Russo A**
CS Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland 20892.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, **(1988 Dec 5)** 263 (34) 17921-4.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 198903
AB 2-Ethyl-1-hydroxy-2,5,5-trimethyl-3-oxazolidine (OXANOH), the one-electron reduction product of the stable **nitroxide** radical, 2-ethyl-2,5,5-trimethyl-3-oxazolidinoxyl (OXANO), is reportedly oxidized by superoxide, and its oxidation has been proposed as a method for assaying superoxide. We find that superoxide can both reduce OXANO and oxidize OXANOH. The respective rate constants, k1 and k2, were determined using two superoxide-generating systems (xanthine oxidase/xanthine as well as ionizing radiation). OXANOH oxidation and OXANO reduction are both inhibitable by superoxide dismutase, pH-dependent (4.5-9.3), and result in a steady state distribution of [OXANO] and [OXANOH], independent of their initial concentrations, i.e. the OXANO/OXANOH couple exhibits a metal-independent superoxide dismutase-like function. Thus it provides a prototype for future development of improved low molecular weight superoxide dismutase mimics which will also function in cellular hydrophobic (aprotic) compartments such as membranes.
CT Check Tags: Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.
Hydrogen-Ion Concentration
Kinetics
Mathematics
Models, Theoretical
Oxazoles
Oxidation-Reduction
***Superoxide Dismutase: ME, metabolism**
Superoxides
RN 11062-77-4 (Superoxides); 65162-38-1 (2-ethyl-2,5,5-trimethyl-3-oxazolidinoxyl); 67201-43-8 (2-ethyl-1-hydroxy-2,5,5-trimethyl-3-oxazolidine)
CN **EC 1.15.1.1 (Superoxide Dismutase)**; 0 (Oxazoles)

L151 ANSWER 54 OF 58 MEDLINE
AN 88330912 MEDLINE
DN 88330912
TI Hydroxyl radical production by stimulated neutrophils reappraised.
AU Samuni A; Black C D; **Krishna C M**; Malech H L; Bernstein E F; **Russo A**
CS Radiation Oncology Branch, National Cancer Institute, Bethesda, Maryland..
SO JOURNAL OF BIOLOGICAL CHEMISTRY, **(1988 Sep 25)** 263 (27) 13797-801.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 198812
AB Release of active oxygen species during the human neutrophil respiratory burst is thought to be mandatory for effective defense against bacterial infections and may play an important role in damage to host tissues. Part of the critical bacterial and host tissue damage has been attributed to hydroxyl radicals produced from superoxide and hydrogen peroxide. Because of the short life time of the very reactive hydroxyl radical, direct study of hydroxyl radical production is not possible; therefore, indirect detection methods such as electron spin resonance (ESR) coupled with appropriate spin-trapping agents such as 5,5-dimethyl-1-pyrroline-N-oxide (DMPO) have been used. Superoxide production during the oxidative burst has been unambiguously demonstrated. Recent reports claim that hydroxyl radicals are not made during neutrophil stimulation and offer as an

explanation the presence of granular components that interfere with hydroxyl radical production. When using the spin-trap agent DMPO, absence of the relatively long-lived adducts DMPO-OH and DMPO-CH3 has been assumed to be prima facie evidence for lack of hydroxyl radical participation. We show that high superoxide flux produced during stimulation of human neutrophils rapidly destroys both DMPO-OH and DMPO-CH3. In accord with previous implications, our results provide an alternative explanation for the absence of .OH adduct in spin-trapping studies and corroborate results obtained using other methods that implicate hydroxyl radical production during neutrophil stimulation.

CT Check Tags: Comparative Study; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.

Cyclic N-Oxides
Electron Spin Resonance Spectroscopy
Free Radicals
*Hydroxides: BL, blood
Neutrophils: DE, drug effects
*Neutrophils: ME, metabolism
Spin Labels
Superoxides: BL, blood
Tetradecanoylphorbol Acetate: PD, pharmacology
Zymosan: PD, pharmacology

RN 11062-77-4 (Superoxides); 16561-29-8 (Tetradecanoylphorbol Acetate); 3317-61-1 (5,5-dimethyl-1-pyrroline-1-oxide); 3352-57-6 (Hydroxyl Radical); 9010-72-4 (Zymosan)

CN **0 (Cyclic N-Oxides)**; 0 (Free Radicals); 0 (Hydroxides); 0 (Spin Labels)

L151 ANSWER 55 OF 58 MEDLINE
AN 88227191 MEDLINE
DN 88227191
TI Effect of non-volatile scavengers of hydroxyl radicals on thymine radical formation induced by gamma-rays and ultrasound.
AU Kondo T; **Krishna C M**; Riesz P
CS Radiation Oncology Branch, National Cancer Institute, Bethesda, Maryland 20892.
NC 1 F05 TW 03764-01 (FIC)
SO INTERNATIONAL JOURNAL OF RADIATION BIOLOGY AND RELATED STUDIES IN PHYSICS, CHEMISTRY AND MEDICINE, **(1988 Jun)** 53 (6) 891-9.
Journal code: GSV. ISSN: 0020-7616.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 198809
AB In order to investigate the mechanism of sonolysis of nucleic acid constituents, the yield of thymine radicals generated by 50 kHz ultrasound in Ar-saturated aqueous solution was compared with that formed by gamma-radiolysis in N2O-saturated solutions in the presence of various non-volatile scavengers, which cannot act in the gas phase of the cavitation bubbles. For comparison of thymine radical yields by sonolysis and gamma radiolysis, the method of spin trapping with 3,5-dibromo-4-nitrosobenzenesulphonate (a water-soluble, non-volatile, aromatic nitroso spin trap) combined with ESR was used. The efficiency of OH radical scavenging is expressed by the reciprocal value of C1/2, the scavenger concentration at which the thymine radical yield is decreased by 50 per cent. In gamma radiolysis the scavenging efficiencies of the solutes depend on their rate constants with OH radicals. For sonolysis the C1/2 values were similar to those obtained for gamma radiolysis except for the hydrophobic 5,5-dimethyl-1-pyrroline-N-oxide. These results suggest that thymine radicals induced by ultrasound are produced in the bulk of the solution as well as in the interfacial region.
CT Check Tags: Support, U.S. Gov't, P.H.S.
Azides
Carboxylic Acids
Cobalt Radioisotopes

Cyclic N-Oxides
Electron Spin Resonance Spectroscopy
Free Radicals
Gamma Rays
Glucose
Hydroxides
Potassium Iodide
Solutions
*Thymine
Thymine: RE, radiation effects
*Ultrasonics
Water: RE, radiation effects
RN 14280-30-9 (hydroxide ion); 26628-22-8 (Sodium Azide); 3317-61-1 (5,5-dimethyl-1-pyrroline-1-oxide); 50-99-7 (Glucose); 65-71-4 (Thymine); 7681-11-0 (Potassium Iodide); 7732-18-5 (Water)
CN 0 (Azides); 0 (Carboxylic Acids); 0 (Cobalt Radioisotopes); **0 (Cyclic N-Oxides)**; 0 (Free Radicals); 0 (Hydroxides); 0 (Solutions)

L151 ANSWER 56 OF 58 MEDLINE
AN 88005155 MEDLINE
DN 88005155
TI A new approach for EPR detection of hydroxyl radicals by reaction with sterically hindered cyclic amines and oxygen.
AU Rosenthal I; **Krishna C M**; Yang G C; Kondo T; Riesz P
CS Division of Contaminant Chemistry, Center for Food Safety and Applied Nutrition, Washington, DC 20204..
SO FEBS LETTERS, **(1987 Sep 28)** 222 (1) 75-8.
Journal code: EUH. ISSN: 0014-5793.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 198801
AB Sterically hindered cyclic amines react with hydroxyl radicals in the presence of oxygen to yield stable **nitroxide** radicals which can be detected by EPR. This reaction provides a nonconventional spin-trapping tool for detection of hydroxyl radicals.
CT *Amines
Electron Spin Resonance Spectroscopy: MT, methods
Free Radicals
*Hydroxides: AN, analysis
*Spin Labels
RN 3352-57-6 (Hydroxyl Radical)
CN 0 (Amines); 0 (Free Radicals); 0 (Hydroxides); 0 (Spin Labels)

L151 ANSWER 57 OF 58 MEDLINE
AN 87016995 MEDLINE
DN 87016995
TI On the spin trapping and ESR detection of oxygen-derived radicals generated inside cells.
AU Samuni A; Carmichael A J; **Russo A**; **Mitchell J B**; Riesz P
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1986 Oct)** 83 (20) 7593-7.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 198701
AB Recently several attempts to identify oxygen-derived radicals in whole cells by spin trapping and electron spin resonance have been reported by using 5,5-dimethyl-1-pyrroline-N-oxide as the spin trap. In the present study, the feasibility of this method is examined. Chinese hamster V79 cells and human erythrocytes served as the test systems, while OH radicals were generated by gamma radiolysis. Several spin traps were used to

scavange the radicals and a distinction between exo- and endocellular ESR observable species was achieved using tri(oxalato) chromiate(III) as a line broadening agent. To distinguish between exo- and endocellular sites of radical formation, we studied the effects of high molecular weight scavengers (polyethylene glycols), which do not enter the cell. Various possible obstacles associated with trapping and detecting the radicals inside the cells were examined. The results indicate that the primary radicals react with the spin traps. However, these spin adducts decayed within the cells. Cellularly induced decay of 2-hydroxy-5,5-dimethyl-1-pyrrolidinyloxyl radical presented the major difficulty in detecting the endogenous radicals, and potential experimental approaches to overcome this difficulty are discussed.

CT Check Tags: Animal; Human
Cell Line
Cyclic N-Oxides: DU, diagnostic use
Electron Spin Resonance Spectroscopy
Free Radicals
Hamsters
*Hydroxides: AN, analysis
Molecular Weight
Polyethylene Glycols: PD, pharmacology
*Superoxides: AN, analysis

RN 11062-77-4 (Superoxides); 3317-61-1 (5,5-dimethyl-1-pyrroline-1-oxide); 3352-57-6 (Hydroxyl Radical)

CN **0 (Cyclic N-Oxides)**; 0 (Free Radicals); 0 (Hydroxides); 0 (Polyethylene Glycols)

L151 ANSWER 58 OF 58 MEDLINE

AN 85200052 MEDLINE

DN 85200052

TI Differences in the reduction kinetics of incorporated spin labels in undifferentiated and differentiated mouse neuroblastoma cells.

AU Chen K Y; McLaughlin M G

NC CA 24479-05 (NCI)
RR 7058-15 (NCRR)

SO BIOCHIMICA ET BIOPHYSICA ACTA, **(1985 May 30)** 845 (2) 189-95.
Journal code: A0W. ISSN: 0006-3002.

CY Netherlands

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 198509

AB Significant differences in the rate of reduction of two spin labels, 5-doxylstearic acid and **TEMPOL**, in the undifferentiated and differentiated NB-15 mouse neuroblastoma cells were demonstrated by using electron paramagnetic resonance (EPR) spectroscopy. The half-time (T1/2) values for decay of the EPR signal of 5-doxylstearic acid in the undifferentiated and differentiated neuroblastoma cells were 70 min and 290 min, respectively. The T1/2 values of **TEMPOL** in the undifferentiated and differentiated cells were 18 min and 34 min, respectively. The cellular reductant was characterized as non-protein-bound sulfhydryl groups. A corresponding difference in the cellular non-protein-bound sulfhydryl content, 19.30 nmol/mg protein for the undifferentiated cells and 6.78 nmol/mg protein for the differentiated cells, was observed. Comparison of the reduction rates of **TEMPOL** , 5-doxylstearic acid and 16-doxylstearic acid in the undifferentiated NB-15 cells suggested that the permeation of non-protein-bound sulfhydryl compounds from the cytosol to membrane may be responsible for the reduction of the lipid-soluble stearic acid spin labels.

CT Check Tags: Animal; Comparative Study; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Cell Differentiation
Cell Line
Cell Membrane: ME, metabolism
***Cyclic N-Oxides: ME, metabolism**
Electron Spin Resonance Spectroscopy

Half-Life
Kinetics
Mice
***Neuroblastoma: ME, metabolism**
Neuroblastoma: PA, pathology
Oxidation-Reduction
Spin Labels
Sulfhydryl Compounds: ME, metabolism
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 29545-48-0 (5-doxylstearic acid); 53034-38-1 (16-nitroxystearic acid)
CN **0 (Cyclic N-Oxides)**; 0 (Spin Labels); 0 (Sulfhydryl Compounds)

=> fil biosis

FILE 'BIOSIS' ENTERED AT 11:44:15 ON 28 OCT 2000
COPYRIGHT (C) 2000 BIOSIS(R)

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 25 October 2000 (20001025/ED)

The BIOSIS file has been reloaded. Enter HELP RLOAD and HELP REINDEXING
for details.

=> d his l152-

(FILE 'MEDLINE' ENTERED AT 11:40:04 ON 28 OCT 2000)

FILE 'BIOSIS' ENTERED AT 11:40:35 ON 28 OCT 2000
L152 259 S L1 OR L2 OR L104
L153 205 S TEMPOL
L154 340 S L152,L153
L155 229 S L154 AND PY<=1997
L156 54 S L155 AND 2400?/CC
L157 11 S L155 AND 24010/CC
L158 54 S L156,L157
L159 14 S L158 AND 00520/CC
L160 14 S L158 AND (CONGRESS OR CONFERENCE OR POSTER OR SYMPOS? OR MEET
L161 14 S L159,L160
L162 40 S L158 NOT L161
L163 39 S L162 AND *240?/CC
L164 54 S L161-L163

FILE 'BIOSIS' ENTERED AT 11:44:15 ON 28 OCT 2000

=> d all tot

L164 ANSWER 1 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1997:347915 BIOSIS
DN PREV199799647118
TI Induction of apoptosis in vitro and in vivo by the cholinergic neurotoxin ethylcholine aziridinium.
AU Rinner, W. A.; Pifl, C.; Lassmann, H.; Hoertnagl, H. (1)
CS (1) Inst. Biochemical Pharmacol., Univ. Vienna, Borschkeg. 8a, A-1090 Vienna Austria
SO Neuroscience, (1997) Vol. 79, No. 2, pp. 535-542.
ISSN: 0306-4522.
DT Article
LA English
AB The patterns of cell death induced by the cholinergic neurotoxin ethylcholine aziridinium have been investigated in vitro and in vivo. In

vitro, the drug induced apoptosis both in neuronal SK-N-MC cells (human neuroblastoma cells) and in non-neuronal 293 cells (a human embryonic kidney cell line). Apoptosis was developed maximally between 15 and 24 h of exposure to ethylcholine aziridinium (100 mu-M). At the ultrastructural level apoptotic cells were characterized by condensation and margination of nuclear chromatin, fragmentation of nuclei and the formation of apoptotic bodies. Inhibition of endonuclease by zinc almost completely prevented the occurrence of apoptosis. The free radical scavenger **Tempol** effectively inhibited ethylcholine aziridinium-induced apoptosis by 78.6+-10.3% (n=4), whereas cycloheximide and actinomycin D were only partially effective. In vivo, following injection of ethylcholine aziridinium (2 nmol) into the lateral ventricle of rat brain a high incidence of apoptotic cells as verified by in situ tailing was visible in the periventricular tissue. Neurons as well as glia were affected by the neurotoxin. The number of apoptotic cells peaked two to three days after injection of ethylcholine aziridinium and declined thereafter. Up to one week after ethylcholine aziridinium no signs for the induction of apoptosis in the medial septal nucleus were found. This study provides clear evidence that a neurotoxic compound that induces programmed cell death in vitro is likely to have the same capacity in vivo. Yet, in the case of ethylcholine aziridinium, both the in vitro and the in vivo induction of programmed cell death appears to be an additional feature of ethylcholine aziridinium, which may be independent of the well-established degenerative effect of ethylcholine aziridinium on the cholinergic septohippocampal pathway. The present data indicate that ethylcholine aziridinium provides a useful tool to study molecular mechanisms of neuronal apoptosis.

CC Biochemical Studies - General *10060
Nervous System - General; Methods *20501
Toxicology - General; Methods and Experimental *22501
Neoplasms and Neoplastic Agents - General *24002

BC Hominidae 86215
Muridae *86375

IT Major Concepts
Biochemistry and Molecular Biophysics; Nervous System (Neural Coordination); Oncology (Human Medicine, Medical Sciences); Toxicology

IT Miscellaneous Descriptors
APOPTOSIS; BRAIN; CHOLINERGIC NEUROTOXIN; EMBRYONIC KIDNEY CELL; ETHYLCHOLINE AZIRIDINIUM; IN VITRO; IN VIVO; NERVOUS SYSTEM; NEUROBLASTOMA CELL

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
rat (Muridae); SK-N-MC (Hominidae): cell line; 293 (Hominidae): cell line

ORGN Organism Superterms
animals; chordates; humans; mammals; nonhuman mammals; nonhuman vertebrates; primates; rodents; vertebrates

L164 ANSWER 2 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS

AN 1997:347274 BIOSIS

DN PREV199799646477

TI Suppression of nitric oxide-induced apoptosis by N-acetyl-L-cysteine through modulation of glutathione, bcl-2, and bax protein levels.

AU Ho, Yuan-Soon; Lee, Horng-Mo; Mou, Tung-Chang; Wang, Ying-Jan; Lin, Jen-Kun (1)

CS (1) Inst. Biochem., Coll. Med., Natl. Taiwan Univ., Number 1, Sec. 1, Jen-Ai Rd., Taipei Taiwan

SO Molecular Carcinogenesis, (1997) Vol. 19, No. 2, pp. 101-113. ISSN: 0899-1987.

DT Article

LA English

AB It has been demonstrated that nitric oxide (NO) can promote apoptosis in human cancer cells. To test the protective effects of antioxidants (N-acetyl-L-cysteine (LNAC)) and free-radical spin traps

(5,5-dimethyl-1-pyrroline N-oxide and 2,2,6,6,-tetramethyl-1-piperidinyloxy) against NO-induced apoptosis, a human colon cancer cell line (COLO 205) was treated with NO, and its survival rate was evaluated both with and without antioxidant therapy. LNAC arrested the development of progression of apoptosis in COLO 205 cells in a dose-dependent manner, promoted long-term survival, and prevented the internucleosomal DNA cleavage induced by NO. The intracellular level of glutathione (GSH) was found to be elevated in cells after exposure to LNAC. The bax protein levels were elevated by NO treatment, and this effect was blocked by LNAC. On the other hand, the compared to cells that received NO pretreatment. In summary, our results suggest that the protective effect of LNAC may be linked to its inducement of increases in cellular GSH and bcl-2 protein levels and to its suppression of cellular bax protein in treated cells.

CC Cytology and Cytochemistry - Human *02508
Biochemical Studies - General *10060
Biophysics - General Biophysical Studies *10502
Digestive System - General; Methods *14001
Endocrine System - General *17002
Neoplasms and Neoplastic Agents - General *24002
BC Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Digestive System (Ingestion and Assimilation); Endocrine System (Chemical Coordination and Homeostasis); Oncology (Human Medicine, Medical Sciences)
IT Chemicals & Biochemicals
NITRIC OXIDE; N-ACETYL-L-CYSTEINE; GLUTATHIONE; 2,2,6,6-TETRAMETHYL-1-PIPERIDINYLOXY
IT Miscellaneous Descriptors
ANTIOXIDANT; BAX PROTEIN; BCL-2 PROTEIN; DIGESTIVE SYSTEM; FREE-RADICAL SPIN TRAP; GLUTATHIONE; HUMAN COLON CANCER CELLS; MODULATION; N-ACETYL-L-CYSTEINE; NITRIC OXIDE; TUMOR BIOLOGY; 2,2,6,6-TETRAMETHYL-1-PIPERIDINYLOXY; 5,5-DIMETHYL-1-PYRROLINE-N-OXIDE
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
COLO 205 (Hominidae): cell line
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 10102-43-9 (NITRIC OXIDE)
616-91-1 (N-ACETYL-L-CYSTEINE)
70-18-8 (GLUTATHIONE)
2564-83-2 (2,2,6,6-TETRAMETHYL-1-PIPERIDINYLOXY)

L164 ANSWER 3 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1997:231500 BIOSIS
DN PREV199799530703
TI DNA damage and apoptosis in human leukemic cells treated with the piperidine nitroxide **TEMPOL**.
AU Monti, E. (1); Gariboldi, M. B.; Supino, R.; Piccinini, F.
CS (1) Inst. Pharmacology, Univ. Milan, Milan Italy
SO **Proceedings of the American Association for Cancer Research Annual Meeting**, (1997) Vol. 38, No. 0, pp. 193.
Meeting Info.: **Eighty-eighth Annual Meeting of the American Association for Cancer Research** San Diego, California, USA April 12-16, 1997
ISSN: 0197-016X.
DT **Conference; Abstract**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Human *02508
Genetics and Cytogenetics - Human *03508
Pathology, General and Miscellaneous - Necrosis *12510
Pathology, General and Miscellaneous - Therapy *12512
Pharmacology - Clinical Pharmacology *22005
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy

***24008**
BC Hominidae *86215
IT Major Concepts
Cell Biology; Genetics; Oncology (Human Medicine, Medical Sciences); Pathology; Pharmacology
IT Chemicals & Biochemicals
PIPERIDINE NITROXIDE; 4-HYDROXY-2,2,6,6-TETRAMETHYLPIPERIDINE-N-OXYL
IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; APOPTOSIS; BLOOD AND LYMPHATIC DISEASE; CELL CYCLE; CYTOTOXICITY; DNA DAMAGE; DNA FRAGMENTATION; LEUKEMIA; NEOPLASTIC DISEASE; PHARMACOLOGY; PIPERIDINE NITROXIDE; TUMOR BIOLOGY; 4-HYDROXY-2,2,6,6-TETRAMETHYLPIPERIDINE-N-OXYL
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
HL-60 (Hominidae): cell line; KG-1 (Hominidae): cell line
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 6146-40-3 (PIPERIDINE NITROXIDE)
2226-96-2 (4-HYDROXY-2,2,6,6-TETRAMETHYLPIPERIDINE-N-OXYL)

L164 ANSWER 4 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1997:216337 BIOSIS
DN PREV199799522841
TI Evaluation of **Tempol** radioprotection in a murine tumor model.
AU Hahn, Stephen M.; Sullivan, Francis J.; Deluca, Anne Marie; Krishna, C. Murali; Wersto, Nancy; Venzon, David; Russo, Angelo; Mitchell, James B. (1)
CS (1) Radiation Biol. Branch, Natl. Cancer Inst., 9000 Rockville Pike, Build. 10, Room B3B69, Bethesda, MD 20892 USA
SO Free Radical Biology & Medicine, (1997) Vol. 22, No. 7, pp. 1211-1216. ISSN: 0891-5849.
DT Article
LA English
AB **Tempol**, a stable nitroxide free radical compound, is an in vitro and in vivo radioprotector. Previous studies have shown that **Tempol** protects C3H mice against whole-body radiation-induced bone marrow failure. In this study, the radioprotection of tumor tissue was evaluated. RIF-1 tumor cells were implanted in female C3H mice 10 d prior to radiation. Groups of mice were injected intraperitoneally with **Tempol** (275 mg/kg) or PBS followed 10 min later by a single dose of radiation to the tumor bed. Tumor growth curves generated after 10 and 33.3 Gy doses of radiation showed no difference in growth between the **Tempol**- and PBS-treated animals. A full radiation dose-response experiment revealed a tumor control dose in 50% of the animals in 30 d (TCD-50/30) value of 36.7 Gy for **Tempol**-treated mice and 41.8 Gy for saline-treated mice suggesting no protection of the RIF-1 tumor by **Tempol**. Tumor pharmacokinetics were done to determine why **Tempol** differentially protected bone marrow and not tumor cells. Differential reduction of **Tempol** in the RIF-1 tumor and bone marrow was evaluated with EPR spectroscopy 10, 20, and 30 min after injection. Bioreduction of **Tempol** to its corresponding hydroxylamine (which is not a radioprotector) occurred to a greater extent in RIF-1 tumor cells compared to bone marrow. We conclude that the differences in radioprotection may result from enhanced intratumor bioreduction of **Tempol** to its nonradioprotective hydroxylamine analogue. The nitroxides as a class of compounds may provide a means to exploit the redox differences between normal tissues and tumors.
CC Radiation - Radiation Effects and Protective Measures *06506
Biochemical Studies - General *10060
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Pharmacology - General *22002
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Neoplasms and Neoplastic Agents - Pathology; Clinical Aspects;

Systemic Effects *24004
BC Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Pharmacology; Radiation Biology; Tumor Biology
IT Chemicals & Biochemicals
TEMPOL; NITROXIDE; 4-HYDROXY-2,2,6,6-TETRAMETHYLPIPERIDINE-N-OXYL
IT Miscellaneous Descriptors
ANIMAL MODEL; BLOOD AND LYMPHATICS; BONE MARROW; CANCER; C3H; FEMALE; NEOPLASTIC DISEASE; PHARMACOKINETICS; PHARMACOLOGY; RADIOPROTECTION; RADIOPROTECTORANT; RADIOSENSITIVITY; REGROWTH; RIF-1 CELL LINE; STABLE NITROXIDE FREE RADICAL COMPOUND; **TEMPOL**; TRANSPLANTATION; TUMOR BIOLOGY; 4-HYDROXY-2,2,6,6-TETRAMETHYLPIPERIDINE-N-OXYL
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates
RN **2226-96-2** (**TEMPOL**)
13408-29-2 (NITROXIDE)
2226-96-2 (4-HYDROXY-2,2,6,6-TETRAMETHYLPIPERIDINE-N-OXYL)

L164 ANSWER 5 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1997:24738 BIOSIS
DN PREV199799323941
TI Modulatory effect of **tempol** on toxicity and antitumor activity of 6-mercaptopurine and on P450 cytochrome level.
AU Konovalova, N. P. (1); Diatchkovskaya, R. F.; Volkova, L. M.; Varfolomeev, V. N.
CS (1) Inst. Chemical Physics, Russian Academy Sci., Chernogolovka, Moscow Region 142 432 Russia
SO Neoplasma (Bratislava), (1996) Vol. 43, No. 5, pp. 341-346.
ISSN: 0028-2685.
DT Article
LA English
AB Low selectivity of contemporary antitumor drugs requires a search for its improvement. In this context nitroxyl radicals are of interest as promising pharmacological agents. The introduction of nitroxyl radical into the structure of antitumor cytostatics was found to reduce considerably their general and specific toxicity. In this work, we demonstrate a detoxifying effect of **tempol** upon its combined injection with cytostatics at their absolute lethal dose in the intact mice as well as an improvement of sensitivity of tumor-bearing animals to 6-MP. **Tempol** is shown to normalize the level of oxidized form of P450 cytochrome in a liver, reduced as a result of the injection of 6-MP.
CC Biochemical Studies - General *10060
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Enzymes - Physiological Studies *10808
Digestive System - Physiology and Biochemistry *14004
Pharmacology - General *22002
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Toxicology - Pharmacological Toxicology *22504
Neoplasms and Neoplastic Agents - Pathology; Clinical Aspects; Systemic Effects *24004
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Digestive System (Ingestion and Assimilation); Enzymology (Biochemistry and Molecular Biophysics); Pharmacology; Toxicology; Tumor Biology
IT Chemicals & Biochemicals
TEMPOL; 6-MERCAPTOPURINE; P450; NITROXYL

IT Miscellaneous Descriptors
ADVERSE EVENT; ANTIDOTE-DRUG; ANTINEOPLASTIC AGENT; ANTITUMOR ACTIVITY; DETOXIFYING EFFECT; DIGESTIVE SYSTEM; LIVER; MODULATORY EFFECT; NITROXYL RADICAL; OXIDIZED FORM; PHARMACOLOGY; P450 CYTOCHROME; **TEMPOL**; TOXICOLOGY; TUMOR BIOLOGY; 6-MERCAPTOPURINE
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates
RN **2226-96-2 (TEMPOL)**
50-44-2 (6-MERCAPTOPURINE)
9035-51-2 (P450)
14332-28-6 (NITROXYL)

L164 ANSWER 6 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1996:271622 BIOSIS
DN PREV199698827751
TI Adjunctive treatment of murine neuroblastoma with 6-hydroxydopamine and **Tempol**.
AU Purpura, Patti; Westman, Laurel; Will, Patricia; Eidelman, Anthony; Kagan, Valerian E.; Osipov, Anatoly N.; Schor, Nina Felice (1)
CS (1) Div. Child Neurology, Children's Hosp. Pittsburgh, 3705 Fifth Avenue, Pittsburgh, PA 15213 USA
SO Cancer Research, (1996) Vol. 56, No. 10, pp. 2336-2342.
ISSN: 0008-5472.
DT Article
LA English
AB Currently available therapy for disseminated neuroblastoma affords only a 5-20% 5-year survival rate. We have attempted to design targeted chemotherapy for this disease by exploiting the dopamine uptake system on neuroblastoma cells. 6-Hydroxydopamine (6OHDA) is a neurotransmitter analogue, which generates cytolytic oxygen radicals in neuroblastoma cells that take it up. It is, however, predictably, systemically toxic, because of its spontaneous oxidation. Its toxicity is particularly severe in the sympathetic nervous system, because this tissue selectively concentrates dopamine and its analogues. Lowering the dose of 6OHDA below toxic levels prohibitively compromises its antitumor effect. To avoid both the systemic and sympathetic nervous system toxicity yet retain the antitumor efficacy of 6OHDA, we have used the antioxidant **Tempol** adjunctively with 6OHDA. Administration of **Tempol** (250 mg/kg, i.p.) 10 min prior to administration of toxic doses of 6OHDA (350 or 400 mg/kg, i.p.) resulted in a decrease in the mortality rate, sympathetic nervous system impairment, and activity impairment compared with those seen with 6OHDA alone. Tumor weights from mice administered saline or **Tempol** alone were 3.6 +- 1.9 and 2.9 +- 0.7 g, respectively. In contrast, mice administered **Tempol** followed by 6OHDA had an average tumor weight of 0.7 +- 0.3 g. Tumor incidence was also reduced from 80-100% to 40%. Studies performed using electron spin resonance spectroscopy suggest that **Tempol** acts in this system by reacting directly with both the 6OHDA radical and, in the presence of iron, its oxidation product, the hydroxyl radical.
CC Biochemical Studies - General 10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Pathology, General and Miscellaneous - Therapy 12512
Nervous System - Pathology *20506
Pharmacology - Endocrine System *22016
Pharmacology - Neuropharmacology *22024
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Muridae *86375
IT Major Concepts
Nervous System (Neural Coordination); Pharmacology; Tumor Biology
IT Chemicals & Biochemicals

6-HYDROXYDOPAMINE; **TEMPOL**
IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; ANTIOXIDANT AGENT; **TEMPOL**; 6-HYDROXYDOPAMINE
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Muridae (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; rodents; vertebrates
RN 1199-18-4 (6-HYDROXYDOPAMINE)
2226-96-2 (**TEMPOL**)

L164 ANSWER 7 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1996:110379 BIOSIS
DN PREV199698682514
TI Nitroxide radicals, modificators of toxic action of cytostatics.
AU Konovalova, N. P.
CS Inst. Chem. Phys., Russ. Acad. Sci., Chernogolovka Russia
SO Voprosy Onkologii (St. Petersburg), (1995) Vol. 41, No. 2, pp. 49-50. ISSN: 0507-3758.
DT Article
LA Russian
CC Biochemical Studies - General *10060
Enzymes - General and Comparative Studies; Coenzymes *10802
Pathology, General and Miscellaneous - Therapy *12512
Digestive System - General; Methods *14001
Pharmacology - General *22002
Toxicology - General; Methods and Experimental *22501
Neoplasms and Neoplastic Agents - General *24002
BC Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Digestive System (Ingestion and Assimilation); Enzymology (Biochemistry and Molecular Biophysics); Pathology; Pharmacology; Toxicology; Tumor Biology
IT Chemicals & Biochemicals
NITROXIDE; **TEMPOL**; CYCLOPHOSPHAMIDE; THIOTEPA; 6-MERCAPTOPURINE; CYTOCHROME P-450; NITROXYL
IT Miscellaneous Descriptors
CYCLOPHOSPHAMIDE; LIVER CYTOCHROME P-450; NITROXYL RADICAL; NOTE; **TEMPOL**; THIOTEPA; 6-MERCAPTOPURINE
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
rat (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates
RN 13408-29-2 (NITROXIDE)
2226-96-2 (**TEMPOL**)
50-18-0 (CYCLOPHOSPHAMIDE)
52-24-4 (THIOTEPA)
50-44-2 (6-MERCAPTOPURINE)
9035-51-2 (CYTOCHROME P-450)
14332-28-6 (NITROXYL)

L164 ANSWER 8 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1996:63875 BIOSIS
DN PREV199698636010
TI Modulation of sensitivity to mitomycin C and a dithiol analogue by **tempol** in non-small-cell lung cancer cell lines under hypoxia.
AU Bando, Takuma (1); Kasahara, Kazuo; Shibata, Kazuhiko; Numata, Yuka; Heki, Utako; Shirasaki, Hiroki; Iwasa, Kei-Ichi; Fujimura, Masaki; Matsuda, Tamotsu
CS (1) Third Dep. Internal Med., Kanazawa Univ. Sch. Med., 13-1 Takara-machi,

Kanazawa 920 Japan
SO Journal of Cancer Research and Clinical Oncology, (1996) Vol. 122, No. 1, pp. 21-26.
ISSN: 0171-5216.
DT Article
LA English
AB We examined the mechanisms involved in the bioactivation of mitomycin C (MMC) and a newly developed MMC analogue: 7-N-(2-((2-(gamma-L-glutamylamino)ethyl)dithio)ethyl)mitomycin C, KW-2149, in non-small-cell lung cancer (NSCLC) cell lines under aerobic and hypoxic conditions. To investigate these mechanisms, we used MMC-resistant non-small-cell lung cancer cell lines (PC-9/MC4) that had been established in our laboratory from the parent PC-9 cell line by continuous exposure to MMC. We previously reported that the MMC-resistant cell line (PC-9/MC4) was poor in NAD(P)H dehydrogenase (quinone) activity and approximately 6-fold more resistant than the parent cells (PC-9) to MMC on 2-h exposure under aerobic conditions. In this study, the subline PC-9/MC4 was 6.7-fold more resistant to MMC than PC-9, the parent cell line, under aerobic conditions, and 5.2-fold more resistant under hypoxic conditions after 2 h exposure to MMC. However, on co-incubation with **tempol**, an inhibitor of the one-electron reduction pathway, the sensitivity of PC-9/MC4 to MMC was impaired under hypoxic conditions, but the impairment was not evident under aerobic conditions. KW-2149, the newly developed MMC analogue, was cytotoxic for both PC-9/MC4 and PC-9 cells, and the sensitivity of both cell lines to KW-2149 was not changed by exposure to hypoxic conditions or by coincubation with **tempol**. There were no significant differences in the intracellular uptake of MMC and the activities of cytosolic detoxification enzymes between the PC-9 and PC-9/MC4 cell lines. These results support the hypothesis that the one-electron reduction pathway plays a partial role in the bioactivation of MMC, but not of KW-2149, and that KW-2149 is excellent at circumventing resistance to MMC in NSCLC.
CC Genetics and Cytogenetics - Human *03508
Biochemistry - Gases 10012
Biochemical Studies - General 10060
Pathology, General and Miscellaneous - Therapy 12512
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Respiratory System *22030
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Hominidae *86215
IT Major Concepts
Genetics; Oncology (Human Medicine, Medical Sciences); Pharmacology
IT Chemicals & Biochemicals
MITOMYCIN C; **TEMPOL**
IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; MITOMYCIN C
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 50-07-7 (MITOMYCIN C)
2226-96-2 (TEMPOL)

L164 ANSWER 9 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:496637 BIOSIS
DN PREV199598520187
TI Decreased sensitivity of multidrug-resistant tumor cells to cisplatin is correlated with sorcin gene co-amplification.
AU Demidova, N. S.; Ilyinskaya, G. V.; Shirayaeva, O. A.; Chernova, O. B.; Goncharova, S. A.; Kopnin, B. P. (1)
CS (1) Inst. Carcinogenesis, Cancer Res. Cent., Russ. Acad. Med. Sci., 115 478 Moscow Russia
SO Neoplasma (Bratislava), (1995) Vol. 42, No. 4, pp. 195-201.

ISSN: 0028-2685.
DT Article
LA English
CC Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - Animal *03506
Biochemical Studies - General 10060
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Minerals 10069
Replication, Transcription, Translation *10300
Pathology, General and Miscellaneous - Therapy 12512
Metabolism - Minerals *13010
Metabolism - Proteins, Peptides and Amino Acids *13012
Metabolism - Nucleic Acids, Purines and Pyrimidines *13014
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
Blood, Blood-Forming Organs and Body Fluids - Blood, Lymphatic and Reticuloendothelial Pathologies *15006
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Pharmacology - General *22002
Pharmacology - Drug Metabolism; Metabolic Stimulators 22003
Pharmacology - Blood and Hematopoietic Agents *22008
Neoplasms and Neoplastic Agents - Neoplastic Cell Lines *24005
Neoplasms and Neoplastic Agents - Biochemistry *24006
Neoplasms and Neoplastic Agents - Carcinogens and Carcinogenesis *24007
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Neoplasms and Neoplastic Agents - Blood and Reticuloendothelial Neoplasms *24010
Laboratory Animals - General 28002
Tissue Culture, Apparatus, Methods and Media 32500
Medical and Clinical Microbiology - Virology *36006
Chemotherapy - Antiviral Agents 38506
Plant Physiology, Biochemistry and Biophysics - Chemical Constituents 51522
Pharmacognosy and Pharmaceutical Botany *54000
BC Papovaviridae 02616
Cricetidae 86310
Muridae *86375
IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cell Biology; Genetics; Infection; Metabolism; Molecular Genetics (Biochemistry and Molecular Biophysics); Pharmacology; Tumor Biology
IT Chemicals & Biochemicals
CISPLATIN; RUBOMYCIN; RUBOXYL; VINBLASTINE; VINCRISTINE; THIOPHOSPHAMIDE; SARCOLYSIN
IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; CISPLATIN; DNA AMPLIFICATION; P-388 LEUKEMIA CELLS; RUBOMYCIN; RUBOXYL; SARCOLYSIN; SV40-TRANSFORMED FIBROBLASTS; THIOPHOSPHAMIDE; VINBLASTINE; VINCRISTINE
ORGN Super Taxa
Cricetidae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Papovaviridae: Viruses
ORGN Organism Name
hamster (Cricetidae); mouse (Muridae); Papovaviridae (Papovaviridae)
ORGN Organism Superterms
animals; chordates; mammals; microorganisms; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates; viruses
RN 15663-27-1 (CISPLATIN)
11016-72-1 (RUBOMYCIN)
84412-94-2 (RUBOXYL)
865-21-4 (VINBLASTINE)
57-22-7 (VINCRISTINE)
52-24-4 (THIOPHOSPHAMIDE)

1465-26-5 (SARCOLYSIN)

L164 ANSWER 10 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:394900 BIOSIS
DN PREV199598409200
TI Effects of antioxidants on fiber mutagenesis.
AU Hei, Tom K.; He, Zhu Y.; Suzuki, Keiji
CS Cent. Radiol. Res., College Physicians Surgeons, Columbia Univ., New York, NY 10032 USA
SO Carcinogenesis (Oxford), (1995) Vol. 16, No. 7, pp. 1573-1578.
ISSN: 0143-3334.
DT Article
LA English
AB Recent studies from this laboratory have shown that asbestos fibers are mutagenic in cultured mammalian cells when assayed using a system that can detect multilocus deletions. Southern analysis of the induced mutants shows that the majority contain large deletions ranging in size from a few thousand to several million basepairs. In the present study, the effects of free radical scavenging enzymes on the cytotoxic and mutagenic potential of chrysotile fibers were examined using the human-hamster hybrid (A-L) cells. Exponentially growing cells were treated with graded doses of fibers for a 24 h period either in the presence or absence of catalase, superoxide dismutase (SOD) or **Tempol**. Fiber-exposed cells were treated with the various enzymes either concurrently with the fiber or extended through the entire expression period. While the survival of A-L cells treated with graded doses of chrysotile fibers with or without a concurrent treatment with SOD and catalase was not significantly different, the mutation yield at the S1 locus was significantly reduced in cells treated with these antioxidant enzymes. Furthermore, cells treated with the enzymes for a prolonged period were not better protected than those treated only during fiber treatment. The SOD mimic nitroxide, **Tempol**, had no effect on either the survival or mutagenic yield of chrysotile fibers. While SOD and catalase reduced the mutagenic potency of asbestos fibers in AL cells, they did not alter the molecular spectrum of fiber-induced mutagenesis. Our results indicate that antioxidant enzymes can protect cells against the genotoxic damages induced by chrysotile fibers, and are highly suggestive of the roles of oxyradicals in the fibrogenic and carcinogenic mechanisms of asbestos fibers.
CC Biochemical Studies - General 10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Enzymes - Physiological Studies *10808
Toxicology - Environmental and Industrial Toxicology *22506
Neoplasms and Neoplastic Agents - Biochemistry *24006
Neoplasms and Neoplastic Agents - Carcinogens and Carcinogenesis *24007
BC Hominidae 86215
Cricetidae *86310
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Oncology (Human Medicine, Medical Sciences); Toxicology
IT Chemicals & Biochemicals
CATALASE; SUPEROXIDE DISMUTASE
IT Miscellaneous Descriptors
ASBESTOS; CARCINOGENESIS; CATALASE; MUTATION; OXYRADICAL; SUPEROXIDE DISMUTASE
ORGN Super Taxa
Cricetidae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
hamster (Cricetidae); human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; nonhuman mammals; nonhuman vertebrates; primates; rodents; vertebrates
RN 9001-05-2 (CATALASE)
9054-89-1 (SUPEROXIDE DISMUTASE)

L164 ANSWER 11 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:255845 BIOSIS
DN PREV199598270145
TI Molecular mechanisms of tirapazamine (SR 4233, WIN 59072)-induced hepatocyte toxicity under low oxygen concentrations.
AU Khan, S. (1); O'Brien, P. J.
CS (1) Fac. Pharmacy, Univ. Toronto, 19 Russell Street, Toronto, ON M5S 2S2 Canada
SO British Journal of Cancer, (1995) Vol. 71, No. 4, pp. 780-785. ISSN: 0007-0920.
DT Article
LA English
AB Previously we showed that tirapazamine (SR 4233, Win 59075) is cytotoxic towards hepatocytes under conditions of hypoxia but not in 10% or 95% oxygen and that bioreduction by DT-diaphorase or cytochrome P450 is not a major pathway. In the present study, we report that tirapazamine is highly cytotoxic to isolated rat hepatocytes maintained under 1% oxygen and the molecular cytotoxic mechanism has been elucidated. Cytotoxicity was prevented by the cytochrome P450 2E1 inhibitors phenyl imidazole, isoniazid, isopropanol or ethanol, suggesting that cytochrome P450 2E1 catalyzed tirapazamine reductive bioactivation. By contrast, dicumarol, a DT-diaphorase inhibitor, markedly increased tirapazamine-induced cytotoxicity. Cytotoxicity was also inhibited in normal but not DT-diaphorase-inactivated hepatocytes by increasing cellular NADH levels with lactate or ethanol or the mitochondrial respiratory inhibitors. Evidence that oxygen activation contributed to cytotoxicity was that glutathione oxidation occurred well before cytotoxicity ensued and that tirapazamine was more cytotoxic towards catalase- or glutathione reductase-inactivated hepatocytes. Furthermore, polyphenolic antioxidants such as quercetin, caffeic acid or purpurogallin, the radical trap **Tempol** or the iron chelator desferrioxamine prevented tirapazamine-mediated cytotoxicity. However, the antioxidants diphenylphenylenediamine, butylated hydroxyanisole or butylated hydroxytoluene did not prevent cytotoxicity and malonaldehyde formation was not increased, suggesting that lipid peroxidation was not important. The above results suggest that DT-diaphorase detoxifies tirapazamine whereas reduced cytochrome P450 reduces tirapazamine to a nitrogen oxide anion radical which forms cytotoxic reactive oxygen species as a result of redox cycling.
CC Cytology and Cytochemistry - Animal *02506
Biochemistry - Gases *10012
Biochemical Studies - General 10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Porphyrins and Bile Pigments 10065
Biochemical Studies - Minerals 10069
External Effects - Pressure 10606
Enzymes - General and Comparative Studies; Coenzymes *10802
Enzymes - Physiological Studies *10808
Pathology, General and Miscellaneous - Therapy 12512
Metabolism - General Metabolism; Metabolic Pathways *13002
Metabolism - Proteins, Peptides and Amino Acids *13012
Metabolism - Porphyrins and Bile Pigments *13013
Digestive System - Pathology *14006
Pharmacology - General *22002
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Digestive System *22014
Toxicology - Pharmacological Toxicology *22504
Toxicology - Antidotes and Preventative Toxicology *22505
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Tissue Culture, Apparatus, Methods and Media 32500
Plant Physiology, Biochemistry and Biophysics - Chemical Constituents 51522
Pharmacognosy and Pharmaceutical Botany *54000
BC Muridae *86375
IT Major Concepts

Biochemistry and Molecular Biophysics; Cell Biology; Digestive System (Ingestion and Assimilation); Enzymology (Biochemistry and Molecular Biophysics); Metabolism; Pharmacology; Toxicology; Tumor Biology
IT Chemicals & Biochemicals
TIRAPAZAMINE; SR 4233; OXYGEN; DT-DIAPHORASE; ISONIAZID; ISOPROPANOL; ETHANOL; QUERCETIN; CAFFEIC ACID; PURPUROGALLIN; **TEMPOL**; DESFERRIOXAMINE
IT Miscellaneous Descriptors
ANTIDOTE-DRUG; ANTINEOPLASTIC-DRUG; CAFFEIC ACID; CYTOCHROME P-450-2E-1; DESFERRIOXAMINE; DT-DIAPHORASE; ETHANOL; ISONIAZID; ISOPROPANOL; PHENYLIMIDAZOLE; PURPUROGALLIN; QUERCETIN; REDOX CYCLING; SR-4233; **TEMPOL**; TIRAPAZAMINE; WIN-59075
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
rat (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates
RN 27314-97-2 (TIRAPAZAMINE)
27314-97-2 (SR 4233)
7782-44-7 (OXYGEN)
9032-20-6 (DT-DIAPHORASE)
54-85-3 (ISONIAZID)
67-63-0 (ISOPROPANOL)
64-17-5 (ETHANOL)
117-39-5 (QUERCETIN)
331-39-5 (CAFFEIC ACID)
569-77-7 (PURPUROGALLIN)
2226-96-2 (TEMPOL)
70-51-9 (DESFERRIOXAMINE)

L164 ANSWER 12 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:237392 BIOSIS
DN PREV199598251692
TI Adjunctive treatment of murine neuroblastoma with 6-hydroxydopamine (OHDA) and **tempol**.
AU Purpura, Patti (1); Westman, Laurel; Will, Patricia; Eidelman, Anthony; Schor, Nina Felice
CS (1) Dep. Ped., Univ. Pittsburgh, Pittsburgh, PA USA
SO Pediatric Research, (1994) Vol. 37, No. 4 PART 2, pp. 164A.
Meeting Info.: **105th Annual Meeting of the American Pediatric Society and the 64th Annual Meeting of the Society for Pediatric Research** San Diego, California, USA May 7-11, 1995
ISSN: 0031-3998.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Biochemical Studies - General *10060
Pathology, General and Miscellaneous - Therapy *12512
Nervous System - Pathology *20506
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Nervous System (Neural Coordination); Pathology; Tumor Biology
IT Chemicals & Biochemicals
6-HYDROXYDOPAMINE; **TEMPOL**
IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; **MEETING ABSTRACT**; **TEMPOL**; 6-HYDROXYDOPAMINE
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
Muridae (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; rodents; vertebrates
RN 1199-18-4 (6-HYDROXYDOPAMINE)
2226-96-2 (TEMPOL)

L164 ANSWER 13 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:186488 BIOSIS
DN PREV199598200788
TI Cytotoxicity of **Tempol**, a piperidine nitroxide spin label, against different neoplastic and non-neoplastic cell lines.
AU Monti, Elena (1); Gariboldi, Marzia (1); Supino, Rosanna; Piccinini, Francesco (1)
CS (1) Inst. Pharmacol., Univ. Milan, Milan Italy
SO **Proceedings of the American Association for Cancer Research Annual Meeting**, (1995) Vol. 36, No. 0, pp. 387.
Meeting Info.: **Eighty-sixth Annual Meeting of the American Association for Cancer Research** Toronto, Ontario, Canada March 18-22, 1995
ISSN: 0197-016X.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Cytology and Cytochemistry - Human *02508
Biochemical Studies - General 10060
Pathology, General and Miscellaneous - Therapy *12512
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
In Vitro Studies, Cellular and Subcellular *32600
BC Hominidae 86215
Rodentia - Unspecified *86265
IT Major Concepts
Cell Biology; Oncology (Human Medicine, Medical Sciences); Pathology; Pharmacology
IT Chemicals & Biochemicals
TEMPOL; PIPERIDINE NITROXIDE
IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; CELL CYCLE EFFECTS; EXPERIMENTAL THERAPEUTICS; **MEETING ABSTRACT**; PHARMACOKINETICS; RODENT CELL LINES; **TEMPOL**
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Rodentia - Unspecified: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae); Rodentia (Rodentia - Unspecified)
ORGN Organism Superterms
animals; chordates; humans; mammals; nonhuman mammals; nonhuman vertebrates; primates; rodents; vertebrates
RN **2226-96-2 (TEMPOL)**
6146-40-3 (PIPERIDINE NITROXIDE)

L164 ANSWER 14 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:912 BIOSIS
DN PREV199598015212
TI Ruboxyl: A daunorubicin analog: First basic and clinical islets.
AU Seminara, P. (1); Franchi, F. (1); Ramirez, R.; Carracedo, J.; Rojas, R.; Rossetti, R.; Konovalova, N.
CS (1) III Clin. Med., Univ. La Sapienza, Roma Italy
SO International Journal of Biological Markers, (1994) Vol. 9, No. 3, pp. 188.
Meeting Info.: **3rd National Meeting of the Italian Society of Applied**

and Basic Cell Kinetics Forli, Italy September 22-24, 1994
ISSN: 0393-6155.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Human 02508
Biochemical Studies - General 10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Carbohydrates 10068
Pathology, General and Miscellaneous - Therapy 12512
Metabolism - Carbohydrates *13004
Metabolism - Proteins, Peptides and Amino Acids *13012
Metabolism - Metabolic Disorders *13020
Blood, Blood-Forming Organs and Body Fluids - Blood and Lymph Studies 15002
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
Blood, Blood-Forming Organs and Body Fluids - Blood, Lymphatic and Reticuloendothelial Pathologies *15006
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Blood and Hematopoietic Agents *22008
Pharmacology - Immunological Processes and Allergy *22018
Neoplasms and Neoplastic Agents - Diagnostic Methods *24001
Neoplasms and Neoplastic Agents - Immunology *24003
Neoplasms and Neoplastic Agents - Neoplastic Cell Lines *24005
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Tissue Culture, Apparatus, Methods and Media 32500
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
BC Hominidae *86215
IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Clinical Immunology (Human Medicine, Medical Sciences); Hematology (Human Medicine, Medical Sciences); Metabolism; Oncology (Human Medicine, Medical Sciences); Pharmacology
IT Chemicals & Biochemicals
RUBOXYL
IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; B-CELL LYMPHOPROLIFERATIVE DISEASE; CHRONIC LYMPHOCYTIC LEUKEMIA; **MEETING ABSTRACT**; **MEETING POSTER**; RUBOXYL; WALDENSTROM'S MACROGLOBULINEMIA CELLS
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN **84412-94-2** (RUBOXYL)

L164 ANSWER 15 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1994:474548 BIOSIS
DN PREV199497487548
TI Novel radiation protectors.
AU Mitchell, James B. (1); Hahn, Stephen (1); Liebmann, James (1); Cook, John (1); Krishna, Murali (1); Russo, Angelo (1); Wink, David
CS (1) Radiation Biol. Branch, Natl. Cancer Inst., Bethesda, MD 20892 USA
SO International Journal of Radiation Oncology Biology Physics, (1994) Vol. 30, No. SUPPL. 1, pp. 101.
Meeting Info.: **36th Annual Meeting of the American Society for Therapeutic Radiology and Oncology** San Francisco, California, USA October 2-6, 1994
ISSN: 0360-3016.

DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Radiation - Radiation and Isotope Techniques *06504
Biochemical Studies - General 10060
Pathology, General and Miscellaneous - Therapy 12512
Pharmacology - Clinical Pharmacology 22005
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Cricetidae 86310
Muridae *86375
IT Major Concepts
Radiology (Medical Sciences); Tumor Biology
IT Chemicals & Biochemicals
TEMPOL; NITRIC OXIDE
IT Miscellaneous Descriptors
CYTOTOXICITY; **MEETING ABSTRACT**; NITRIC OXIDE; PHARMACOLOGIC POTENTIAL; RADIOSENSITIZER-DRUG; **TEMPOL**; TUMOR SENSITIZATION
ORGN Super Taxa
Cricetidae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
hamster (Cricetidae); mouse (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates
RN **2226-96-2** (**TEMPOL**)
10102-43-9 (NITRIC OXIDE)

L164 ANSWER 16 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1994:348245 BIOSIS
DN PREV199497361245
TI In vivo electron paramagnetic resonance spectroscopy-imaging in experimental oncology: The hope and the reality.
AU Ferrari, Marco (1); Quaresima, Valentina; Ursini, Cinzia L.; Alecci, Marcello; Sotgiu, Antonello
CS (1) Dep. Biomedical Sci. Technol., University L'Aquila, 67100 L'Aquila Italy
SO International Journal of Radiation Oncology Biology Physics, (1994) Vol. 29, No. 3, pp. 421-425.
ISSN: 0360-3016.
DT Article
LA English
AB Purpose: Low frequency (280 MHz) electron paramagnetic resonance imaging is a new magnetic resonance technique, still being developed, that can map the in vivo spatial distribution of paramagnetic species such as nitroxide free radicals. The reduction rate of these molecules is affected by oxygen concentration. This paper gives some examples of the use of electron paramagnetic resonance imaging methodology in whole rats in the framework of its possible use in experimental oncology. Methods and Materials: The 280 MHz apparatus based on a cylindrical 16 pole magnet was developed and designed specifically for 50-200 g laboratory animals. It generates the main field and the three field gradients required for three-dimensional (3-D) projections. A pyrrolidine nitroxyl (2,2,5,5,-tetramethylpyrrolidine-1-oxyl-3-carboxylic acid) was injected intravenously in rats to provide an electron paramagnetic resonance signal for in vivo measurements. Electron paramagnetic resonance X-band spectrometer was used to monitor pyrrolidine nitroxyl decay in an external blood circuit during normoxia and moderate hypoxia (15% O-2). Results and Conclusion: One-dimensional (1-D) transversal and longitudinal mapping of this nitroxide free radical distribution in rat whole body was obtained 7-9 min after injection. In circulating blood, nitroxide half-life decreased significantly during hypoxia. The present sensitivity (10-4-10-5 M), spatial resolution (3-10 mm) and collection time (3-5 min) could be drastically improved by narrow

linewidth paramagnetic probes and pulsed techniques.
CC Methods, Materials and Apparatus, General - Photography 01012
Radiation - Radiation and Isotope Techniques *06504
Biochemistry - Gases 10012
Biochemical Studies - General 10060
Biophysics - General Biophysical Techniques 10504
Anatomy and Histology, General and Comparative - Radiologic Anatomy 11106
Pathology, General and Miscellaneous - Diagnostic *12504
Metabolism - General Metabolism; Metabolic Pathways 13002
Metabolism - Energy and Respiratory Metabolism 13003
Cardiovascular System - General; Methods 14501
Blood, Blood-Forming Organs and Body Fluids - Blood and Lymph Studies 15002
Bones, Joints, Fasciae, Connective and Adipose Tissue - General; Methods 18001
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Pharmacology - General *22002
Pharmacology - Drug Metabolism; Metabolic Stimulators 22003
Pharmacology - Connective Tissue, Bone and Collagen - Acting Drugs *22012
Routes of Immunization, Infection and Therapy 22100
Neoplasms and Neoplastic Agents - Diagnostic Methods *24001
BC Muridae *86375
IT Major Concepts
Pathology; Pharmacology; Radiology (Medical Sciences); Skeletal System (Movement and Support); Tumor Biology
IT Chemicals & Biochemicals
2,2,5,5-TETRAMETHYLPYRROLIDINE-1-OXYL-3-CARBOXYLIC ACID
IT Miscellaneous Descriptors
ADENOCARCINOMA; DIAGNOSTIC METHOD; DIAGNOSTIC-DRUG; EPR; FIBROSARCOMA; IN-VIVO; MELANOMA; 2,2,5,5-TETRAMETHYLPYRROLIDINE-1-OXYL-3-CARBOXYLIC ACID
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae); rat (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates
RN **2154-68-9** (2,2,5,5-TETRAMETHYLPYRROLIDINE-1-OXYL-3-CARBOXYLIC ACID)

L164 ANSWER 17 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1994:317850 BIOSIS
DN PREV199497330850
TI Modification of the aerobic cytotoxicity of etanidazole.
AU Palayoor, Sanjeewani T. (1); Bump, Edward A.; Malaker, Kamal; Langley, Ruth E.; Saroff, Daniel M.; Delfs, John R.; Hurwitz, Selwyn J.; Coleman, C. Norman
CS (1) Joint Cent. Radiation Therapy, Harvard Med. Sch., 50 Binney St., Boston, MA 02115 USA
SO International Journal of Radiation Oncology Biology Physics, (1994) Vol. 29, No. 2, pp. 289-293.
ISSN: 0360-3016.
DT Article
LA English
AB Purpose: To determine the feasibility of modifying the aerobic cytotoxicity of etanidazole without interfering with the tumoricidal action of radiation plus etanidazole. Methods and Materials: The aerobic cytotoxicity of etanidazole was studied using two different models: (1) Induction of apoptosis in EL4 cells: apoptotic DNA fragmentation was analyzed by agarose gel electrophoresis following 24 h treatment with etanidazole alone or in combination with various modifiers. (2) Spinal cord neuronal loss in organotypic roller tube cultures: Survival of acetylcholinesterase positive ventral horn neurons was analyzed morphometrically following 72 h treatment with etanidazole alone or in

combination with vitamin E succinate. Results: Etanidazole (10 mM) induced apoptosis in EL4 cells. This effect was suppressed by 24 h treatment with TPA, IBMX, the free radical scavenger **TEMPOL** or vitamin E succinate. Vitamin E succinate also protected spinal cord cultures from etanidazole-induced neuronal loss. Conclusion: These results suggest that it might be possible to modify the neurotoxicity of etanidazole with agents that would not be expected to interfere with the tumoricidal action of radiation plus etanidazole.

CC General Biology - Explorations, Expeditions, etc. *00506
Radiation - Radiation Effects and Protective Measures *06506
Biochemical Studies - General 10060
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Pathology, General and Miscellaneous - Necrosis *12510
Blood, Blood-Forming Organs and Body Fluids - Blood, Lymphatic and Reticuloendothelial Pathologies *15006
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Nervous System - Pathology *20506
Toxicology - Pharmacological Toxicology *22504
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Neoplasms and Neoplastic Agents - Blood and Reticuloendothelial Neoplasms *24010

BC Muridae *86375

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); General Life Studies; Nervous System (Neural Coordination); Pathology; Radiation Biology; Toxicology; Tumor Biology

IT Chemicals & Biochemicals
ETANIDAZOLE

IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; APOPTOTIC DNA FRAGMENTATION; EL4 LYMPHOMA CELLS; ETANIDAZOLE; NEUROTOXICITY; RADIATION

ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
mouse (Muridae)

ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates

RN 22668-01-5 (ETANIDAZOLE)

L164 ANSWER 18 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS

AN 1994:291544 BIOSIS

DN PREV199497304544

TI Protection against hypoxia-mediated SR-4233 cytotoxicity by the stable nitroxide free radical **Tempol**.

AU Herscher, L. L. (1); Krishna, C. M.; Degraff, W.; Mitchell, J. B.; Russo, A.

CS (1) Radiat. Oncol. Branch, Natl. Cancer Inst., Bethesda, MD 20892 USA

SO **Proceedings of the American Association for Cancer Research Annual Meeting**, (1994) Vol. 35, No. 0, pp. 634.
Meeting Info.: **85th Annual Meeting of the American Association for Cancer Research** San Francisco, California, USA April 10-13, 1994
ISSN: 0197-016X.

DT **Conference**

LA English

CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal 02506
Radiation - Radiation and Isotope Techniques 06504
Radiation - Radiation Effects and Protective Measures *06506
Biochemistry - Gases *10012
Biochemical Studies - General 10060
Pathology, General and Miscellaneous - Therapy 12512
Pharmacology - General *22002

Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Neoplasms and Neoplastic Agents - Pathology; Clinical Aspects; Systemic Effects *24004
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Mammalia - Unspecified *85700
IT Major Concepts
Biochemistry and Molecular Biophysics; Pharmacology; Radiation Biology; Tumor Biology
IT Chemicals & Biochemicals
SR-4233; NITROXIDE; **TEMPOL**
IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; **MEETING ABSTRACT**; METABOLIC-DRUG; RADIATION ONCOLOGY; SR-4233; **TEMPOL**
ORGN Super Taxa
Mammalia - Unspecified: Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mammal (Mammalia - Unspecified); Mammalia (Mammalia - Unspecified)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; vertebrates
RN 27314-97-2 (SR-4233)
13408-29-2 (NITROXIDE)
2226-96-2 (TEMPOL)

L164 ANSWER 19 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1994:274139 BIOSIS
DN PREV199497287139
TI Sonochemical activation of hematoporphyrin: An ESR study.
AU Yumita, Nagahiko; Nishigaki, Ryuichiro; Umemura, Koshiro; Morse, Philip D.; Swartz, Harold M.; Cain, Charles A.; Umemura, Shin-Ichiro (1)
CS (1) Advanced Res. Lab., Hitachi Ltd., Hatoyama, Saitama 350 Japan
SO Radiation Research, (1994) Vol. 138, No. 2, pp. 171-176.
ISSN: 0033-7587.
DT Article
LA English
AB The production of 2,2,6,6-tetramethyl-4-piperidone-N-oxyl by reaction of 2,2,6,6-tetramethyl-4-piperidone (TMPone) with ultrasonically generated active species in oxygenated solutions of hematoporphyrin (Hp) was studied by electron spin resonance spectroscopy. The nitroxide production rate in air-saturated TMPone solutions in phosphate-buffered saline of pH 9.0 was significantly higher in the presence of Hp than in its absence. The enhancement of nitroxide production by Hp was significantly inhibited in the presence of sodium azide or histidine in the solution. The production rate with Hp was doubled by substitution of deuterium oxide, while the rate without Hp increased only modestly. These results suggest that a substantial amount of active oxygen can be generated by ultrasound in aqueous solutions of Hp. Since the production rate was not reduced by mannitol and no nitroxide was produced in nitrogen-saturated solutions, it appears that hydroxyl radicals do not account for a major portion of the active oxygen species which reacted with TMPone to yield a nitroxide.
CC Methods, Materials and Apparatus, General - Photography 01012
Radiation - Radiation and Isotope Techniques *06504
Biochemical Methods - General *10050
Biochemical Studies - General *10060
Pathology, General and Miscellaneous - Therapy 12512
Neoplasms and Neoplastic Agents - Pathology; Clinical Aspects; Systemic Effects *24004
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
IT Major Concepts
Biochemistry and Molecular Biophysics; Methods and Techniques; Radiology (Medical Sciences); Tumor Biology
IT Chemicals & Biochemicals
HEMATOPORPHYRIN; 2,2,6,6-TETRAMETHYL-4-PIPERIDONE-N-OXYL; 2,2,6,6-TETRAMETHYL-4-PIPERIDONE; NITROXIDE

IT Miscellaneous Descriptors
ANTINEOPLASTIC THERAPY; NITROXIDE PRODUCTION RATE; SPECTROSCOPY; 2,2,6,6-TETRAMETHYL-4-PIPERIDONE; 2,2,6,6-TETRAMETHYL-4-PIPERIDONE-N-OXYL
RN 14459-29-1 (HEMATOPORPHYRIN)
2896-70-0 (2,2,6,6-TETRAMETHYL-4-PIPERIDONE-N-OXYL)
826-36-8 (2,2,6,6-TETRAMETHYL-4-PIPERIDONE)
13408-29-2 (NITROXIDE)

L164 ANSWER 20 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1994:268355 BIOSIS
DN PREV199497281355
TI Impairments in metabolism of superoxide radicals in liver tissue of tumor-bearing mice during development of Ehrlich ascites carcinoma and the normalizing effect of ruboxyl.
AU Gurevich, S. M.; Vartanyan, L. S.; Nagler, L. G.
CS N.N. Semenov Inst. Chem. Phys., Acad. Sci. Russ., Moscow Russia
SO Voprosy Meditsinskoi Khimii, (1993) Vol. 39, No. 6, pp. 16-20.
ISSN: 0042-8809.
DT Article
LA Russian
SL English
AB Activity of the systems involved in generation and utilization of superoxide radicals was studied in microsomes, mitochondria and nuclei of liver tissue from intact mice, mice with developed Ehrlich ascites carcinoma and of the animals treated with antitumoral drug ruboxyl. The ratio between the rate of superoxide radicals formation and activity of superoxide dismutase (SOD) served as specific characteristic of the O hivin -2 SOD system in the corresponding compartments. During tumoral development, the pattern studied was altered in all the subcellular organelles used, thus demonstrating an impairment of free radical oxidation status in liver tissue of tumor-bearing animals. Administration of ruboxyl into healthy animals led to distinct increase in this ratio in mitochondria, while the drug normalized patterns of the O hivin SOD-2 system in all the cell compartments studied in tumor-bearing animals. Ruboxyl appears to exhibit regulation effect on free radical oxidation.
CC Biochemical Studies - General 10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Enzymes - Physiological Studies *10808
Chordate Body Regions - Abdomen *11314
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Metabolism - General Metabolism; Metabolic Pathways *13002
Digestive System - Physiology and Biochemistry *14004
Neoplasms and Neoplastic Agents - Pathology; Clinical Aspects; Systemic Effects *24004
BC Muridae *86375
IT Major Concepts
Digestive System (Ingestion and Assimilation); Enzymology (Biochemistry and Molecular Biophysics); Metabolism; Morphology; Pathology; Tumor Biology
IT Chemicals & Biochemicals
SUPEROXIDE RADICALS; RUBOXYL; SUPEROXIDE DISMUTASE
IT Miscellaneous Descriptors
FREE RADICAL OXIDATION; SUPEROXIDE DISMUTASE
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Muridae (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; rodents; vertebrates
RN 11062-77-4 (SUPEROXIDE RADICALS)
84412-94-2 (RUBOXYL)
9054-89-1 (SUPEROXIDE DISMUTASE)

L164 ANSWER 21 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1994:259333 BIOSIS
DN PREV199497272333
TI Polymerase chain reaction-directed DNA sequencing of bleomycin-induced "nondeletion"-type, 6-thioguanine-resistance mutants in Chinese hamster ovary cell derivative AS52: Effects of an inhibitor and a mimic of superoxide dismutase.
AU An, Jie (1); Hsie, Abraham W.
CS (1) Dep. Preventive Med. and Community Health, Univ. Tex. Med. Branch, 2.102 Ewing Hall, J-10, Galveston, TX 77555-1010 USA
SO Environmental and Molecular Mutagenesis, (1994) Vol. 23, No. 2, pp. 101-109.
ISSN: 0893-6692.
DT Article
LA English
AB Bleomycin-induced, 6-thioguanine-resistant, 'non deletion' mutants pretreated with or without either TRIEN (triethylenetetramine), a superoxide dismutase (SOD) inhibitor, or **TEMPOL** (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl), a SOD mimic, were analyzed by polymerase chain reaction (PCR)-directed DNA sequencing in a Chinese hamster ovary (CHO) cell derivative, AS52. Among the 23 bleomycin-induced mutants, six have 3-bp 5'-TGA-3' deletions in the region of 366-371, five have single-base deletions, seven have base substitutions, three have insertions, and two have possible translocations. Among the 16 bleomycin-induced mutants pretreated with TRIEN, six have the 5'-TGA-3' deletion (366-371), two have single-base deletions, one has a 13-bp deletion, four have single-base substitutions, one has a double-base substitution, and two have insertions. Among the 17 bleomycin-induced mutants pretreated with **TEMPOL**, six have the same TGA deletions, two have single-base deletions, two have single-base insertions, four have single-base substitutions, one mutant has a 12-bp deletion, one has a 13-bp deletion, and one mutant shows no detectable change in its coding region in the DNA sequence. A possible shift from a ROS-mediated mutational spectrum to a spontaneous mutational spectrum by TRIEN further indicates that reactive oxygen species play an important role in bleomycin mutagenesis in mammalian cells.
CC Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - Animal *03506
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biophysics - Molecular Properties and Macromolecules *10506
Biophysics - Bioenergetics: Electron Transport and Oxidative Phosphorylation *10510
Enzymes - Chemical and Physical *10806
Enzymes - Physiological Studies *10808
Toxicology - Pharmacological Toxicology *22504
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
In Vitro Studies, Cellular and Subcellular *32600
BC Cricetidae *86310
IT Major Concepts
Biochemistry and Molecular Biophysics; Bioenergetics (Biochemistry and Molecular Biophysics); Cell Biology; Enzymology (Biochemistry and Molecular Biophysics); Genetics; Toxicology; Tumor Biology
IT Chemicals & Biochemicals
BLEOMYCIN; 6-THIOGUANINE; SUPEROXIDE DISMUTASE; OXYGEN
IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; BLEOMYCIN; ENVIRONMENTAL MUTAGENESIS; MOLECULAR MUTAGENESIS; REACTIVE OXYGEN SPECIES
ORGN Super Taxa
Cricetidae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Cricetidae (Cricetidae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; rodents; vertebrates
RN 11056-06-7 (BLEOMYCIN)

154-42-7 (6-THIOGUANINE)
9054-89-1 (SUPEROXIDE DISMUTASE)
7782-44-7 (OXYGEN)

L164 ANSWER 22 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1994:229133 BIOSIS
DN PREV199497242133
TI Potential use of nitroxides in radiation oncology.
AU Hahn, Stephen M. (1); Krishna, C. Murali; Samuni, Amram; Degraff, William; Cuscela, Daniel O.; Johnstone, Peter; Mitchell, James B.
CS (1) Radiation Oncology Branch, Natl. Cancer Inst., 9000 Rockville Pike, Building 10, Room B3B69, Bethesda, MD 20892 USA
SO Cancer Research, (1994) Vol. 54, No. 7 SUPPL., pp. 2006S-2010S. ISSN: 0008-5472.
DT General Review
LA English
AB The identification of radioprotectors is an important goal for those involved in radiation oncology and for those interested in the investigation of the mechanisms of radiation cytotoxicity. Recently, a new class of in vitro and in vivo radioprotectors, the nitroxides, has been discovered. The nitroxides are low-molecular-weight stable free radicals which are freely membrane permeable and which have been shown to act as superoxide dismutase mimics. Further investigation of these compounds has shown that a water-soluble nitroxide, **Tempol**, protects cultured Chinese hamster V79 cells from the cytotoxicity caused by superoxide, hydrogen peroxide, and t-butyl hydroperoxide. **Tempol** and rive other water-soluble nitroxides have also been shown to protect V79 cells against radiation-induced cytotoxicity. Potential mechanisms of protection by the nitroxides include oxidation of reduced transition metals, superoxide dismutase-like activity, and scavenging of oxy- and carbon-based free radicals. In vivo studies reveal that **Tempol** protects C3H mice from the lethal effects of radiation with a dose causing 50% lethality within 30 days of 9.97 Gy and 7.84 Gy in **Tempol** -treated and saline-treated mice, respectively, and a dose modification factor of 1.3. The nitroxides represent a new class of non-thiol radioprotectors which may also have application as general antioxidants. Additional work is necessary to screen other nitroxides for in vivo radioprotection and toxicity as well as to fully evaluate the extent to which these compounds protect tumors.
CC Radiation - Radiation and Isotope Techniques *06504
Radiation - Radiation Effects and Protective Measures *06506
Biochemical Studies - General 10060
Pathology, General and Miscellaneous - Therapy 12512
Pharmacology - General *22002
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Muridae *86375
IT Major Concepts
Pharmacology; Radiation Biology; Radiology (Medical Sciences); Tumor Biology
IT Chemicals & Biochemicals
NITROXIDES; **TEMPOL**
IT Miscellaneous Descriptors
RADIOPROTECTORANT-DRUG; **TEMPOL**; TUMOR TREATMENT
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates
RN 13408-29-2D (NITROXIDES)
2226-96-2 (TEMPOL)

L164 ANSWER 23 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1994:113238 BIOSIS

DN PREV199497126238
TI Modifiers of radiation-induced apoptosis.
AU Langley, Ruth E.; Palayoor, Sanjeewani T.; Coleman, C. Norman; Bump, Edward A.
CS Joint Cent. Radiation Therapy, Harvard Med. Sch., Dana Farber Cancer Inst., Boston, MA 02115 USA
SO Radiation Research, (1993) Vol. 136, No. 3, pp. 320-326.
ISSN: 0033-7587.
DT Article
LA English
AB EL4 murine lymphoma cells and F9 murine teratocarcinoma cells undergo apoptosis-like cell death after exposure to ionizing radiation. Apoptosis differs in several ways from classical clonogenic cell killing by radiation. We have tested several modifiers and radiomimetic agents in an effort to determine if the mechanism of induction of apoptosis by radiation differs from the mechanism of classical clonogenic cell killing by radiation, and consequently that these two end points of radiation action might be differentially modifiable. We found that internucleosomal DNA fragmentation, characteristic of apoptosis, can result from treatment of EL4 and F9 cells with agents that have diverse modes of action: tert-butyl hydroperoxide, diazenedicarboxylic acid bis(N,N-piperidide), and etoposide. Hydrogen peroxide did not induce internucleosomal DNA fragmentation at concentrations expected to be produced by the doses of ionizing radiation that we used. Radiation-induced DNA fragmentation could be inhibited by 3-aminobenzamide, dibutryl cyclic AMP, or 4-hydroxy-2,2,6,6,-tetramethylpiperidine-N-oxyl, although in this respect there appear to be marked differences between the cell lines.
CC Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - Animal *03506
Radiation - Radiation and Isotope Techniques *06504
Radiation - Radiation Effects and Protective Measures *06506
Biochemical Methods - Nucleic Acids, Purines and Pyrimidines 10052
Biochemical Studies - General 10060
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Replication, Transcription, Translation *10300
Pathology, General and Miscellaneous - Necrosis *12510
Pathology, General and Miscellaneous - Therapy 12512
Blood, Blood-Forming Organs and Body Fluids - Blood, Lymphatic and Reticuloendothelial Pathologies *15006
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Pharmacology - Blood and Hematopoietic Agents 22008
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Neoplasms and Neoplastic Agents - Blood and Reticuloendothelial Neoplasms *24010
Developmental Biology - Embryology - Morphogenesis, General *25508
Tissue Culture, Apparatus, Methods and Media 32500
In Vitro Studies, Cellular and Subcellular *32600
BC Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Cell Biology; Development; Genetics; Molecular Genetics (Biochemistry and Molecular Biophysics); Pathology; Radiation Biology; Radiology (Medical Sciences); Tumor Biology
IT Chemicals & Biochemicals
3-AMINOBENZAMIDE; DIBUTYRYL CYCLIC AMP; 4-HYDROXY-2,2,6,6,-TETRAMETHYLPIPERIDINE-N-OXYL
IT Miscellaneous Descriptors
DIBUTYRYL CYCLIC AMP; INTERNUCLEOSOMAL DNA FRAGMENTATION; MURINE LYMPHOMA EL4 CELLS; MURINE TERATOCARCINOMA F9 CELLS; RADIOPROTECTORANT IMPLICATIONS; 3-AMINOBENZAMIDE; 4-HYDROXY-2,2,6,6,-TETRAMETHYLPIPERIDINE-N-OXYL
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name

Muridae (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; rodents; vertebrates
RN 3544-24-9 (3-AMINOBENZAMIDE)
362-74-3 (DIBUTYRYL CYCLIC AMP)
2226-96-2 (4-HYDROXY-2,2,6,6,-TETRAMETHYLPIPERIDINE-N-OXYL)

L164 ANSWER 24 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1993:517802 BIOSIS
DN PREV199345116427
TI Protection from radiation-induced alopecia with topical application of nitroxides: Fractionated studies.
AU Cuscela, Daniel; Coffin, Deborah; Muldoon, Rebecca; Glass, Joe; Krishna, Murali C.; Bernstein, Eric; Mitchell, James B.
CS Radiation Biol. Sect., Radiation Oncology Branch, Natl. Cancer Inst., Natl. Inst. Health, Bethesda, MD USA
SO International Journal of Radiation Oncology Biology Physics, (1993) Vol. 27, No. SUPPL. 1, pp. 197.
Meeting Info.: **35th Annual Meeting of the American Society for Therapeutic Radiology and Oncology** New Orleans, Louisiana, USA October 11-15, 1993
ISSN: 0360-3016.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Radiation - Radiation and Isotope Techniques *06504
Radiation - Radiation Effects and Protective Measures *06506
Biochemical Studies - General 10060
Chordate Body Regions - Head 11304
Pathology, General and Miscellaneous - Therapy 12512
Integumentary System - General; Methods 18501
Integumentary System - Pathology *18506
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Integumentary System, Dental and Oral Biology *22020
Routes of Immunization, Infection and Therapy 22100
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Hominidae 86215
Caviidae *86300
IT Major Concepts
Dermatology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences); Pharmacology; Radiation Biology; Radiology (Medical Sciences)
IT Chemicals & Biochemicals
NITROXIDES; **TEMPOL**
IT Miscellaneous Descriptors
ABSTRACT; CANCER TREATMENT; DERMATOLOGICAL-DRUG; GUINEA-PIG; RADIOPROTECTORANT-DRUG; TEMPO; **TEMPOL**
ORGN Super Taxa
Caviidae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae); Caviidae (Caviidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; nonhuman mammals; nonhuman vertebrates; primates; rodents; vertebrates
RN 13408-29-2D (NITROXIDES)
2226-96-2 (**TEMPOL**)

L164 ANSWER 25 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1993:400462 BIOSIS
DN PREV199345059287
TI The radioprotector **tempol** does not decrease radiation-induced RIF tumor control in C3H mice.

AU Hahn, S. M.; Sullivan, F.; Deluca, A. M.; Krishna, M. C.; Glass, J.; Russo, A.; Mitchell, J. B.
CS Radiation Oncology Branch, NCI, NIH, Bethesda, MD USA
SO **Proceedings of the American Association for Cancer Research Annual Meeting**, (1993) Vol. 34, No. 0, pp. 433.
Meeting Info.: **84th Annual Meeting of the American Association for Cancer Research** Orlando, Florida, USA May 19-22, 1993
ISSN: 0197-016X.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Radiation - Radiation Effects and Protective Measures *06506
Biochemical Studies - General *10060
Pathology, General and Miscellaneous - Therapy *12512
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Pathology; Radiation Biology; Tumor Biology
IT Chemicals & Biochemicals
TEMPOL
IT Miscellaneous Descriptors
ABSTRACT; ANTIOXIDANT; RADIOPROTECTORANT; STABLE FREE RADICAL
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Muridae (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; rodents; vertebrates
RN **2226-96-2 (TEMPOL)**

L164 ANSWER 26 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1993:400461 BIOSIS
DN PREV199345059286
TI Stem cell factor (SCF) and **tempol** act in synergy to protect mice from lethal irradiation.
AU Liebmann, J. (1); Deluca, A. M. (1); Epstein, A. (1); Steinberg, S.; Russo, A. (1); Mitchell, J. B. (1)
CS (1) Radiation Oncology Branch, NCI, NIH, Bethesda, MD USA
SO **Proceedings of the American Association for Cancer Research Annual Meeting**, (1993) Vol. 34, No. 0, pp. 433.
Meeting Info.: **84th Annual Meeting of the American Association for Cancer Research** Orlando, Florida, USA May 19-22, 1993
ISSN: 0197-016X.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Radiation - Radiation Effects and Protective Measures *06506
Biochemical Studies - General *10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System 15008
Endocrine System - General *17002
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Radiation Biology; Tumor Biology
IT Chemicals & Biochemicals

TEMPOL
IT Miscellaneous Descriptors
ABSTRACT; CANCER RADIOTHERAPY; RADIOPROTECTORANT; STABLE FREE RADICAL
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Muridae (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; rodents; vertebrates
RN **2226-96-2 (TEMPOL)**

L164 ANSWER 27 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1993:82879 BIOSIS
DN PREV199344037129
TI Chemical radiosensitizers in cancer therapy.
AU Shenoy, Mohan A. (1); Singh, Bam B.
CS (1) Radiation Biol. Biochem. Div., Bhabha Atomic Res. Cent., Trombay, Bombay 400 085 India
SO Cancer Investigation, (1992) Vol. 10, No. 6, pp. 533-551.
ISSN: 0735-7907.
DT General Review
LA English
CC Radiation - Radiation and Isotope Techniques *06504
Radiation - Radiation Effects and Protective Measures *06506
Biochemical Studies - General 10060
Biochemical Studies - Carbohydrates 10068
Pathology, General and Miscellaneous - Therapy 12512
Pharmacology - General *22002
Pharmacology - Clinical Pharmacology *22005
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Hominidae *86215
IT Major Concepts
Oncology (Human Medicine, Medical Sciences); Pharmacology; Radiation Biology; Radiology (Medical Sciences)
IT Chemicals & Biochemicals
TRIACETONEAMINE-N-OXYL; P-NITROACETOPHENONE; MISONIDAZOLE; METRONIDAZOLE; CHLORPROMAZINE; PROCAINE HYDROCHLORIDE; DIAMIDE; NEOARSPHENAMINE; 5-THIO-D-GLUCOSE; 2-DEOXY-D-GLUCOSE; LUCANTHONE; MIRACIL D
IT Miscellaneous Descriptors
ANTINEOPLASTIC- DRUG; CHLORPROMAZINE; DIAMIDE; LUCANTHONE; METRONIDAZOLE; MIRACIL D; MISONIDAZOLE; NEOARSPHENAMINE; P=NITROACETOPHENONE; PROCAINE HYDROCHLORIDE; RADIOSENSITIZER-DRUG; TRIACETONEAMINE-N-OXYL; 2=DEOXY-D-GLUCOSE; 5=THIO-D-GLUCOSE
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN **2896-70-0** (TRIACETONEAMINE-N-OXYL)
100-19-6 (P-NITROACETOPHENONE)
13551-87-6 (MISONIDAZOLE)
443-48-1 (METRONIDAZOLE)
50-53-3 (CHLORPROMAZINE)
51-05-8 (PROCAINE HYDROCHLORIDE)
10465-78-8 (DIAMIDE)
457-60-3 (NEOARSPHENAMINE)
20408-97-3 (5-THIO-D-GLUCOSE)
154-17-6 (2-DEOXY-D-GLUCOSE)
479-50-5 (LUCANTHONE)
548-57-2 (MIRACIL D)

L164 ANSWER 28 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1992:526202 BIOSIS
DN BA94:134277
TI PHOSPHORUS-CONTAINING METABOLITES IN ANTHRACYCLINE-RESISTANT MURINE LEUKEMIA P388 CELLS.
AU SHIRYAEVA O A; SEMENOVA N A; SIBELDINA L A; GONCHAROVA S A; KONOVALOVA N P
CS INST. CHEMICAL PHYSICS, RUSSIAN ACADEMY SCI., 142 432 CHERNOGOLOVKA, MOSCOW REGION, RUSSIA.
SO NEOPLASMA (BRATISL), (1992) 39 (4), 229-232.
CODEN: NEOLA4. ISSN: 0028-2685.
FS BA; OLD
LA English
AB The method of 31P nuclear magnetic resonance was used to study in vivo the level of phosphorus-containing metabolites in P388 leukemia cells sensitive or resistant to rubomycin (daunomycin) and its nitroxyl analog - emoxyl. It was shown that decreased content of phosphomonoesters (PME) is characteristic of the resistant strains in comparison with the parent cells. Rubomycin and emoxyl were established not the affect practically the pool of phosphorus-containing metabolites in the cells of the resistant strains, but caused considerable increase of PME level in the cells of the parent strain.
CC Cytology and Cytochemistry - Animal 02506
Radiation - Radiation and Isotope Techniques 06504
Biochemical Methods - Minerals 10059
Biochemical Studies - General 10060
Biochemical Studies - Minerals 10069
Biophysics - General Biophysical Techniques 10504
Pathology, General and Miscellaneous - Therapy 12512
Metabolism - Minerals *13010
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
Blood, Blood-Forming Organs and Body Fluids - Blood, Lymphatic and Reticuloendothelial Pathologies *15006
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Pharmacology - Drug Metabolism; Metabolic Stimulators 22003
Pharmacology - Blood and Hematopoietic Agents *22008
Neoplasms and Neoplastic Agents - Neoplastic Cell Lines *24005
Neoplasms and Neoplastic Agents - Biochemistry *24006
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Neoplasms and Neoplastic Agents - Blood and Reticuloendothelial Neoplasms *24010
Tissue Culture, Apparatus, Methods and Media 32500
BC Muridae 86375
IT Miscellaneous Descriptors
MOUSE DAUNOMYCIN EMOXYL ANTINEOPLASTIC-DRUG PHOSPHORUS-31 NMR ANALYTICAL METHOD PHOSPHOMONOESTERS
RN 7723-14-0 (PHOSPHORUS)
7723-14-0 (PHOSPHORUS-31)
20830-81-3 (DAUNOMYCIN)
84412-94-2 (EMOXYL)

L164 ANSWER 29 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1992:404184 BIOSIS
DN BR43:60059
TI MODULATION OF DOXORUBICIN ADR AND STREPTONIGRIN STN CYTOTOXICITY IN CHINESE HAMSTER V79 CELLS BY A STABLE NITROXIDE FREE RADICAL **TEMPOL** TP.
AU KRISHNA M C; HAHN S M; DE GRAFF W; SAMUNI A; MITCHELL J B; RUSSO A
CS RADIATION ONCOL. BRANCH, NCI, NIH, BETHESDA, MD.
SO 83RD ANNUAL **MEETING** OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, SAN DIEGO, CALIFORNIA, USA, MAY 20-23, 1992. PROC AM ASSOC CANCER RES ANNU **MEET**. (1992) 33 (0), 509.
CODEN: PAMREA.
DT **Conference**
FS BR; OLD

LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Biochemical Studies - General 10060
Enzymes - Physiological Studies *10808
Metabolism - Energy and Respiratory Metabolism *13003
Cardiovascular System - Heart Pathology *14506
Pharmacology - General *22002
Toxicology - Pharmacological Toxicology *22504
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Cricetidae 86310
IT Miscellaneous Descriptors
ABSTRACT ANTINEOPLASTIC-DRUG SUPEROXIDE DISMUTASE CARDIOTOXICITY
RN **2226-96-2** (**TEMPOL**)
3930-19-6 (STREPTONIGRIN)
9054-89-1 (SUPEROXIDE DISMUTASE)
13408-29-2 (NITROXIDE)
23214-92-8 (DOXORUBICIN)

L164 ANSWER 30 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1992:282603 BIOSIS
DN BA94:7253
TI **TEMPOL** A STABLE FREE RADICAL IS A NOVEL MURINE RADIATION PROTECTOR.
AU HAHN S M; TOCHNER Z; KRISHNA C M; GLASS J; WILSON L; SAMUNI A; SPRAGUE M; VENZON D; GLATSTEIN E; MITCHELL J B; RUSSO A
CS RADITION ONCOL. BRANCH/NATIONAL CANCER INST., BUILDING 10, ROOM B3-B69, BETHESDA, MD. 20892.
SO CANCER RES, (1992) 52 (7), 1750-1753.
CODEN: CNREA8. ISSN: 0008-5472.
FS BA; OLD
LA English
AB Nitroxide compounds are stable free radicals which were previously investigated as hypoxic cell radiosensitizers. The stable nitroxide 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl (**Tempol**) has recently been shown to protect aerated cells in culture against superoxide generated from hypoxanthine/xanthine oxidase, hydrogen peroxide, and radiation-induced cytotoxicity and to modestly sensitize hypoxic cultured cells. To extend these observations from the cellular level to the whole animal, the toxicity, pharmacology, and in vivo radioprotective effects of **Tempol** were studied in C3H mice. The maximum tolerated dose of **Tempol** administered i.p. was found to be 275 mg/kg, which resulted in maximal **Tempol** levels in whole blood 5-10 min after injection. Mice were exposed to whole-body radiation in the absence or presence of injected **Tempol** (275 mg/kg) 5-10 min after administration. **Tempol** treatment provided significant radioprotection ($P < 0.0001$); the dose of radiation at which 50% of **Tempol**-treated mice die at 30 days was 9.97 Gy, versus 7.84 Gy for control mice. **Tempol** represents a new class of in vivo, non-sulfur-containing radiation protectors. Given the potential for hypoxic radiosensitization and aerobic cell radioprotection, **Tempol** or other analogues may have potential therapeutic application.
CC Cytology and Cytochemistry - Animal *02506
Radiation - Radiation and Isotope Techniques *06504
Radiation - Radiation Effects and Protective Measures *06506
Biochemistry - Gases *10012
Biochemical Studies - General 10060
Biophysics - Molecular Properties and Macromolecules 10506
Enzymes - Physiological Studies 10808
Pathology, General and Miscellaneous - Necrosis 12510
Pathology, General and Miscellaneous - Therapy 12512
Metabolism - General Metabolism; Metabolic Pathways 13002

Metabolism - Energy and Respiratory Metabolism *13003
Pharmacology - General *22002
Routes of Immunization, Infection and Therapy 22100
Toxicology - Pharmacological Toxicology 22504
Neoplasms and Neoplastic Agents - Neoplastic Cell Lines *24005
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Tissue Culture, Apparatus, Methods and Media 32500
BC Muridae 86375
IT Miscellaneous Descriptors
MOUSE RADIOPROTECTORANT-DRUG HYPOXIC RADIOSENSITIZATION ANTINEOPLASTIC-DRUG
RN **2226-96-2 (TEMPOL)**

L164 ANSWER 31 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1992:206299 BIOSIS
DN BR42:99374
TI MOLECULAR EVIDENCE FOR REACTIVE OXYGEN SPECIES IN BLEOMYCIN MUTAGENESIS IN MAMMALIAN CELLS.
AU AN J; HSIE A W
CS DEP. PREVENTIVE MED. COMMUNITY HEALTH, UNIV. TEXAS MED. BRANCH, GALVESTON, TEXAS 77550.
SO 23RD ANNUAL SCIENTIFIC **MEETING** OF THE ENVIRONMENTAL MUTAGEN SOCIETY, RENO/SPARKS, NEVADA, USA, MARCH 15-19, 1992. ENVIRON MOL MUTAGEN SUPPL. (1992) 0 (20), 2.
CODEN: EMMSEA.
DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Genetics and Cytogenetics - Animal *03506
Biochemistry - Gases *10012
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Chemical and Physical *10806
Metabolism - Nucleic Acids, Purines and Pyrimidines *13014
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Toxicology - General; Methods and Experimental *22501
Toxicology - Pharmacological Toxicology *22504
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy 24008
In Vitro Studies, Cellular and Subcellular 32600
BC Cricetidae 86310
IT Miscellaneous Descriptors
ABSTRACT CHINESE HAMSTER OVARY CHO CELLS HYPOXANTHINE GUANINE PHOSPHORIBOSYL TRANSFERASE LOCUS TRIMETHYLENETETRAMINE 4 HYDROXY-2 2 6 6-TETRAMETHYLPIPERIDINE-1-OXYL SUPEROXIDE DISMUTASE HYDROGEN PEROXIDE DELETION MUTANT
RN **2226-96-2** (4 HYDROXY-2 2 6 6-TETRAMETHYLPIPERIDINE-1-OXYL)
5722-27-0 (TRIMETHYLENETETRAMINE)
7722-84-1 (HYDROGEN PEROXIDE)
7782-44-7 (OXYGEN)
9016-12-0 (HYPOXANTHINE GUANINE PHOSPHORIBOSYL TRANSFERASE)
9054-89-1 (SUPEROXIDE DISMUTASE)
11056-06-7 (BLEOMYCIN)

L164 ANSWER 32 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1992:144490 BIOSIS
DN BA93:78715
TI NEWLY FORMED CHROMOSOME-LIKE STRUCTURES IN INDEPENDENT MOUSE P388 SUBLINES WITH DEVELOPED IN-VIVO MDR1 GENE AMPLIFICATION.
AU DEMIDOVA N S; CHERNOVA O B; SIYANOVA E Y; GONCHAROVA A S; KOPNIN B P
CS INST. CHEMICAL PHYSICS CHERNOGOLOVKA, ACADEMY SCI., KASHIRSKOVE SHOSSE 24, MOSCOW 115478.

SO SOMATIC CELL MOL GENET, (1991) 17 (6), 581-590.
CODEN: SCMGDN. ISSN: 0740-7750.
FS BA; OLD
LA English
AB Mouse leukemia P388 sublines that acquired the resistance to multiple drugs as a result of treatment in vivo with anthracyclines (rubomycin, ruboxyl) and/or vincristine were studied. The mdr gene amplification was found in all tested cell lines: in four of five sublines all three members of the mdr gene family showed increased copy numbers, and in one cell line, developed after treatment with ruboxyl, mdr1a and mdr1b genes were amplified to the same degree, whereas the mdr2 gene was not amplified at all. The levels of amplification of mdr genes varied in different cell lines from 30-fold to 50-fold. Unusual cytological manifestations-relatively large newly formed chromosomelike structures, were revealed in four of five long-term independent sublines. Some of these structures did not contain C blocks; the others, in contrast, were enriched by C-heterochromatin. In situ hybridization showed the presence of mdr genes in newly formed bodies. In the majority of cases, the formation of chromosomelike structures was preceded by the appearance of other, smaller size, structes: the so-called "small chromatin bodies" (minichromosomes) and/or homogeneously G-positive small ring chromosomes.
CC Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - Animal *03506
Biochemical Studies - General 10060
Biophysics - Molecular Properties and Macromolecules *10506
Pathology, General and Miscellaneous - Therapy *12512
Pharmacology - Clinical Pharmacology 22005
Pharmacology - Blood and Hematopoietic Agents *22008
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Neoplasms and Neoplastic Agents - Blood and Reticuloendothelial Neoplasms *24010
BC Muridae 86375
IT Miscellaneous Descriptors
RUBOXYL RUBOMYCIN VINCRISTINE ANTINEOPLASTIC-DRUG LEUKEMIA
RN 57-22-7 (VINCRISTINE)
11016-72-1 (RUBOMYCIN)
84412-94-2 (RUBOXYL)

L164 ANSWER 33 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1992:121249 BIOSIS
DN BA93:67049
TI FRACTIONAL INCORPORATION OF RADIONUCLEOTIDES A MARKER OF IN-VITRO TUMOR CELL CHEMOSENSITIVITY IN COLORECTAL CANCER.
AU FRANCHI F; SEMINARA P; GIANNARELLI D; KONOVALOVA N
CS VIA DI S. AGNESE 12, I-00198 ROMA, ITALY.
SO ONCOLOGY (BASEL), (1991) 48 (6), 510-516.
CODEN: ONCOBS. ISSN: 0030-2414.
FS BA; OLD
LA English
AB Working with the antimetabolic chemopredictivity assay on short term cultures we evidenced a correlation between in vitro chemosentitivity of colorectal cancer and fractional incorporation of radionucleotides. Four different drugs (5-FU, mitomycin C, 4'-iododeoxydoxorubicin and ruboxyl, a nitroxyl derivative of daunorubicin) were tested on 102 tumor cultures. The extent of 3H-TdR and 3H-UdR incorporation into DNA and RNA in the related control cultures was in relationship with the chemosensitivity of the tumor. Along with the labeling index this simple metobalic-kinetic trait may gain a role for the screening of tumor phenotypes sensitive to chemotherapy.
CC Radiation - Radiation and Isotope Techniques *06504
Pathology, General and Miscellaneous - Therapy *12512
Digestive System - Pathology *14006
Pharmacology - Clinical Pharmacology 22005
Pharmacology - Digestive System *22014
Neoplasms and Neoplastic Agents - Pathology; Clinical Aspects;

Systemic Effects *24004
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Tissue Culture, Apparatus, Methods and Media 32500
BC Hominidae 86215
IT Miscellaneous Descriptors
HUMAN RUBOXYL 4 IODODEOXYDOXORUBICIN 5 FLUOROURACIL MITOMYCIN C ANTINEOPLASTIC-DRUG CELL CULTURE
RN 50-07-7 (MITOMYCIN C)
51-21-8 (5 FLUOROURACIL)
84412-94-2 (RUBOXYL)

L164 ANSWER 34 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1992:98575 BIOSIS
DN BA93:55125
TI MECHANISMS OF HYPOXIC AND AEROBIC CYTOTOXICITY OF MITOMYCIN C IN CHINESE HAMSTER V79 CELLS.
AU KRISHNA M C; DEGRAFF W; TAMURA S; GONZALEZ F J; SAMUNI A; RUSSO A; MITCHELL J B
CS RADIATION ONCOLOGY BRANCH, CLINICAL ONCOLOGY PROGRAM, NATIONAL CANCER INST., NIH, BETHESDA, MARYLAND 20892, USA.
SO CANCER RES, (1991) 51 (24), 6622-6628.
CODEN: CNREA8. ISSN: 0008-5472.
FS BA; OLD
LA English
AB Mitomycin C (MMC) induced aerobic and hypoxic cytotoxicity in Chinese hamster V79 cells was studied to evaluate the role of the 1-electron versus 2-electron reductive bioactivation. Superoxide dismutase, catalase, and desferal had no protective effects on the aerobic or hypoxic cytotoxicity of MMC, whereas **Tempol** and **Tempol**-H, which are known to interrupt and terminate radical reactions, provided partial protection under aerobic conditions. However, under hypoxic conditions, **Tempol** provided complete protection whereas **Tempol**-H was ineffective. Electron paramagnetic resonance and spin-trapping investigations, designed to study the mechanisms of such protective effects, confirmed that MMC is activated by the human NADPH:cytochrome P-450 oxidoreductase to its semiquinone radical and that, under aerobic conditions, the semiquinone of MMC reduces H2O2 to produce OH radicals as detected by electron paramagnetic resonance-spin trapping with 5,5-dimethyl-1-pyrroline N-oxide. The 1-electron reduced product of MMC was also found of **Tempol**-H by MMC-. was negligible. Cell survival studies and electron paramagnetic resonance observations indicate that the hypoxic cytotoxicity of MMC is mediated by 1-electron activation to its semiquinone intermediate. Under aerobic conditions, the steady state concentration of this intermediate is low due to the facile autooxidation of the semiquinone producing O2-. and H2O2 which are capable of causing oxidative cytotoxicity. **Tempol**, which can accept an electron from reducing radical species, completely inhibited the hypoxic cytotoxicity of MMC indicating MMC-., the semiquinone of MMC as the species responsible for DNA alkylation and selective hypoxic cytotoxicity of MMC. Our results also indicate that the aerobic cytotoxicity is mediated by other processes in addition to the 1-electron mediated activation.
CC Cytology and Cytochemistry - Animal *02506
Biochemical Studies - General 10060
Biophysics - Molecular Properties and Macromolecules 10506
Enzymes - Physiological Studies *10808
Pathology, General and Miscellaneous - Therapy 12512
Metabolism - General Metabolism; Metabolic Pathways *13002
Metabolism - Energy and Respiratory Metabolism *13003
Metabolism - Nucleic Acids, Purines and Pyrimidines *13014
Pharmacology - General *22002
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Clinical Pharmacology 22005
Neoplasms and Neoplastic Agents - Neoplastic Cell Lines *24005
Neoplasms and Neoplastic Agents - Biochemistry *24006

Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Tissue Culture, Apparatus, Methods and Media 32500
BC Hominidae 86215
Cricetidae 86310
IT Miscellaneous Descriptors
HUMAN ANTINEOPLASTIC-DRUG ELECTRON ACTIVATION NADPH CYTOCHROME P-450 OXIDOREDUCTASE HYDROGEN PEROXIDE REDUCTION HYDROXYL RADICAL PRODUCTION DNA ALKYLATION
RN 50-07-7 (MITOMYCIN C)
7722-84-1 (HYDROGEN PEROXIDE)

L164 ANSWER 35 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1991:485306 BIOSIS
DN BA92:119066
TI EFFECT OF RUBOMYCIN DAUNORUBICIN AND ITS NITROXYL ANALOG ON THE FUNCTION OF RAT HEART MITOCHONDRIA.
AU ROGOVA O M; VOLK S E
CS INST. CHEM. PHYS., ACAD. SCI. USSR, CHERNOGOLOVKA, USSR.
SO ANTIBIOT KHIMIOTER, (1991) 36 (5), 18-20.
CODEN: ANKHEW. ISSN: 0235-2990.
FS BA; OLD
LA Russian
AB Changes in the functional parameters of the rat heart mitochondria were studied in time after a single intraperitoneal administration of rubomycin, the rubomycin combination with 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO-OH) and ruboxyl, a nitroxyl derivative of rubomycin. The administration of rubomycin resulted in inhibition of the heart mitochondria bioenergetic functions (a decrease in the respiration control coefficient, RCC, and the respiration rate, RR, on phosphorilation) during respiration in the presence of NAD+-dependent substrates 6 to 24 hours after the administration. Later the mitochondria functions recovered while in 2 to 3 weeks a secondary decrease in the RCC and RR was observed. During respiration in the presence of succinate the inhibitory effect on the antibiotics was higher. The combined administration of rubomycin and TEMPO-OH eliminated the primary inhibition. In the presence of ruboxyl the inhibitory effect in regard to the NAD+-dependent substrates was not detected. The mechanisms of the toxic action of the anthracycline antibiotics are discussed.
CC Cytology and Cytochemistry - Animal *02506
Biochemical Studies - General 10060
Cardiovascular System - Heart Pathology *14506
Pharmacology - General *22002
Toxicology - Pharmacological Toxicology *22504
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Muridae 86375
IT Miscellaneous Descriptors
RUBOXYL ANTINEOPLASTIC-DRUG TOXICITY
RN 11016-72-1 (RUBOMYCIN)
20830-81-3 (DAUNORUBICIN)
84412-94-2 (RUBOXYL)

L164 ANSWER 36 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1991:389266 BIOSIS
DN BA92:66581
TI SUBRENAL CAPSULE ASSAY OF HUMAN TUMOR CHEMOSENSITIVITY.
AU KONOVALOVA N P; DIATCHKOVSKAYA R F; GANIEVA L KH; VOLKOVA L M; LAPSHIN I M; RUDAKOV B YA; SHAPOSHNIKOV YU G; SHAPIRO A B
CS INST. CHEMICAL PHYSICS., USSR ACAD. SCIENCES, 142 432 CHERNOGOLOVKA, MOSCOW REGION, USSR.
SO NEOPLASMA (BRATISL), (1991) 38 (3), 275-284.
CODEN: NEOLA4. ISSN: 0028-2685.
FS BA; OLD
LA English
AB Breast and colon tumor response to emoxyl, a nitroxyl derivative of

daunomycin, was detected using human tumor heterotransplantation under the renal capsule of immunocompetent mice. The substitution of adrianycin by emoxyl in the combined therapy led to enhanced therapeutic efficacy. The evidence of enhanced response of breast tumors to emoxyl obtained during the histologic examination of xenografts is in good agreement with measurements of tumor fragment weight. It is suggested to use a quantitative kinetic index .vkappa. calculated by the method of equivalent exponents for objective evaluation of tumor response to the drugs.

CC Biochemical Studies - General 10060
Anatomy and Histology, General and Comparative - Regeneration and Transplantation *11107
Pathology, General and Miscellaneous - Therapy *12512
Digestive System - Pathology *14006
Urinary System and External Secretions - General; Methods 15501
Reproductive System - Pathology *16506
Pharmacology - Clinical Pharmacology 22005
Pharmacology - Digestive System *22014
Pharmacology - Reproductive System; Implantation Studies *22028
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008

BC Hominidae 86215
Muridae 86375

IT Miscellaneous Descriptors
MOUSE EMOXYL ADRIAMYCIN ANTINEOPLASTIC-DRUG BREAST CANCER COLON CANCER XENOGRAFT

RN **84412-94-2** (EMOXYL)
23214-92-8Q, 25316-40-9Q (ADRIAMYCIN)

L164 ANSWER 37 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1990:287429 BIOSIS
DN BA90:18275
TI COMPARATIVE STUDY OF THE CYTOTOXIC EFFECT OF ANTHRACYCLINE ANTIBIOTICS ON HETEROTRANSPLANTS OF HUMAN BREAST CANCER CELLS CULTIVATED IN DIFFUSION CHAMBERS IN-VIVO.
AU KRUTOVA T V; KORMAN D B; BATOMUNKUEVA T V
CS INST. CHEM. PHYS., ACAD. SCI. USSR, MOSCOW, USSR.
SO ANTIBIOT KHIMIOTER, (1989) 34 (11), 849-852.
CODEN: ANKHEW. ISSN: 0235-2990.
FS BA; OLD
LA Russian
AB Cytotoxic activity of doxorubicin, daunomycin, carminomycin and ruboxyl against 50 human breast cancer heterotransplants in diffusion chambers was studied. The effect was estimated, autoradiographically on the 6th or the 7th day of the cultivation after the drug administration in the maximum tolerance doses. The tumors were considered sensitive when the labeling index of their transplants after the treatment appeared to be reduced by 50 or less per cent against the control. The number of the tumors sensitive to all the drugs amounted to 72-80 per cent. 19 tumors were sensitive to 4 antibiotics. 14 and 8 tumors were sensitive to 3 and 2 antibiotics, respectively, and only 1 tumor was sensitive to 1 drug. The sensitivity significantly correlated with the initial labeling index of the primary tumors and their heterotransplants. The results suggested that daunomycin and ruboxyl possessed a high cytotoxic activity close to that of doxorubicin and carminomycin and might be recommended for clinical trials in the treatment of patients with breast cancer.

CC Cytology and Cytochemistry - Human *02508
Biochemical Studies - General 10060
Anatomy and Histology, General and Comparative - Regeneration and Transplantation 11107
Pathology, General and Miscellaneous - Therapy *12512
Reproductive System - General; Methods 16501
Reproductive System - Pathology *16506
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Reproductive System; Implantation Studies *22028
Neoplasms and Neoplastic Agents - Pathology; Clinical Aspects; Systemic Effects *24004

Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Hominidae 86215
IT Miscellaneous Descriptors
RUBOXYL CARMINOMYCIN DOXORUBICIN DAUNOMYCIN ANTINEOPLASTIC-DRUG
RN 20830-81-3 (DAUNOMYCIN)
23214-92-8 (DOXORUBICIN)
39472-31-6 (CARMINOMYCIN)
84412-94-2 (RUBOXYL)

L164 ANSWER 38 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1990:125727 BIOSIS
DN BR38:59937
TI CHEMOTHERAPEUTIC SENSITIVITY OF HUMAN TUMOR XENOGRAFTS TO NITROXYL DERIVATIVE OF ANTHRACYCLINE.
AU KONOVALOVA N P; DIATCHKOVSKAYA R F
CS INST. CHEM. PHYSICS USSR ACAD. OF SCI., CHERNOGOLOVKA, MOSCOW REGION, USSR.
SO SIXTH NCI-EORTC (NATIONAL CANCER INSTITUTE-EUROPEAN ORGANIZATION FOR RESEARCH ON TREATMENT OF CANCER) **SYMPOSIUM** ON NEW DRUGS IN CANCER THERAPY, AMSTERDAM, NETHERLANDS, MARCH 7-10, 1989. INVEST NEW DRUGS. (1989) 7 (4), 393.
CODEN: INNDDK. ISSN: 0167-6997.
DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Human 02508
Biochemical Studies - General 10060
Pathology, General and Miscellaneous - Therapy 12512
Reproductive System - Pathology *16506
Pharmacology - Reproductive System; Implantation Studies *22028
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Hominidae 86215
IT Miscellaneous Descriptors
ABSTRACT EMOXYL ADRIAMYCIN RUBOMYCIN CYCLOPHOSPHAMIDE 5 FLUOROURACIL ANTINEOPLASTIC-DRUG BREAST CARCINOMA
RN 50-18-0 (CYCLOPHOSPHAMIDE)
51-21-8 (5 FLUOROURACIL)
11016-72-1 (RUBOMYCIN)
14332-28-6D (NITROXYL)
84412-94-2 (EMOXYL)
23214-92-8Q, 25316-40-9Q (ADRIAMYCIN)

L164 ANSWER 39 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1990:5780 BIOSIS
DN BA89:5780
TI THE STUDY OF PHOSPHORUS-CONTAINING METABOLITES IN ANTHRACYCLINE-RESISTANT MURINE LEUKEMIA P388 CELLS.
AU SHIRYAEVA O A; SEMENOVA N A; SIBEL'DINA L A; GONCHAROVA S A; KONOVALOVA N P
CS DIV., INST. CHEM. PHYS., ACAD. SCI. USSR, CHERNOGOLOVKA, USSR.
SO EKSP ONKOL, (1989) 11 (4), 70-73.
CODEN: EKSODD. ISSN: 0204-3564.
FS BA; OLD
LA Russian
AB The method of 31P nuclear magnetic resonance has been used to study in vivo the level of phosphorus-containing metabolites in cells of two strains of murine leukemia P388 with the phenotype of the multidrug resistance and in cells of the parent strain. Cells of both resistant strains showed a depressed level of phosphomonoesters in comparison with the parent one. The influence of rubomycin and emoxyl on the level of phosphorus-containing metabolites of drug-resistant and -sensitive strains has been evaluated. The drugs were established not to affect practically

the pool of these metabolites of the resistant strains. Both drugs significantly increased the pool of phosphomonoesters in the parent strain cells.

CC Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - Animal *03506
Radiation - Radiation and Isotope Techniques *06504
Biochemical Studies - Minerals 10069
Biophysics - General Biophysical Techniques 10504
Metabolism - Minerals *13010
Blood, Blood-Forming Organs and Body Fluids - Blood, Lymphatic and Reticuloendothelial Pathologies *15006
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Neoplasms and Neoplastic Agents - Biochemistry *24006
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Neoplasms and Neoplastic Agents - Blood and Reticuloendothelial Neoplasms *24010

IT Miscellaneous Descriptors
PHENOTYPE RUBOMYCIN EMOXYL ANTINEOPLASTIC-DRUG NMR

RN 7723-14-0 (PHOSPHORUS)
11016-72-1 (RUBOMYCIN)
84412-94-2 (EMOXYL)

L164 ANSWER 40 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1989:406851 BIOSIS
DN BA88:76276
TI CHEMOTHERAPEUTICAL SENSITIVITY OF THE ANTHRACYCLINE-RESISTANT STRAINS OF MICE LEUKEMIA P388.
AU DEMIDOVA N S; GONCHAROVA S A; SHIRYAEVA O A; KONOVALOVA N P
CS DEP., INST. CHEM. PHYS., ACAD. SCI. USSR, CHERNOGOLOVKA, USSR.
SO EKSP ONKOL, (1989) 11 (1), 65-68.
CODEN: EKSODD. ISSN: 0204-3564.
FS BA; OLD
LA Russian
AB P388 leukemia strains resistant to rubomycin and ruboxylnitroxyl derivative of rubomycin were studied for their drug sensitivity. The resistant strains exhibited cross resistance to anthracycline antibiotics, vinca alkaloids, actinomycin D, colchicine. The rubomycin-resistant strain gained significantly higher sensitivity (in comparison with the parent strain and the ruboxyl-resistant strain) to six drugs: cisplatin, sarcolysin, dopan, thiophosphamide, degranol, 6-mercaptopurine. The karyotype of the ruboxyl-resistant cells was characterized by the presence of chromosome with homogeneously staining region (HSR). The alteration of the HSR-location was accompanied by the increase of chemotherapeutical sensitivity of the ruboxylresistant strain to the alkylating agents.

CC Microscopy Techniques - Cytology and Cytochemistry 01054
Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - Animal *03506
Biochemical Methods - Nucleic Acids, Purines and Pyrimidines 10052
Biochemical Studies - General 10060
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biochemical Studies - Minerals 10069
Biophysics - Molecular Properties and Macromolecules *10506
Neoplasms and Neoplastic Agents - Pathology; Clinical Aspects; Systemic Effects *24004
Neoplasms and Neoplastic Agents - Neoplastic Cell Lines *24005
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008

BC Muridae 86375

IT Miscellaneous Descriptors
CISPLATIN SARCOLYSIN DOPAN THIOPHOSPHAMIDE DEGRANOL 6 MERCAPTOPURINE ANTINEOPLASTIC-DRUG RUBOXYL-RESISTANT CELL PHENOTYPE CHROMOSOME ANALYSIS HOMOGENOUS STAINING REGION CYTOGENETICS

RN 50-44-2 (6 MERCAPTOPURINE)
52-24-4 (THIOPHOSPHAMIDE)

520-09-2 (DOPAN)
551-74-6 (DEGRANOL)
1465-26-5 (SARCOLYSIN)
15663-27-1 (CISPLATIN)
84412-94-2 (RUBOXYL)

L164 ANSWER 41 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1989:75427 BIOSIS
DN BA87:39825
TI SUSCEPTIBILITY OF HETEROTRANSPLANTS FROM HUMAN TUMORS TO SPIN-LABELLED RUBROMYCIN DERIVATIVE.
AU KONOVALOVA N P; D'YACHKOVSKAYA R F; GANIEVA L KH; VOLKOVA L M; LAPSHIN I M; RUDAKOV B YA; SHAPOSHNIKOV YU G
CS DEP., INST. CHEM. PHYS., ACAD. SCI. USSR, CHERNOGOLOVKA, USSR.
SO EKSP ONKOL, (1988) 10 (4), 54-59.
CODEN: EKSODD. ISSN: 0204-3564.
FS BA; OLD
LA Russian
AB A degree of emoxyl activity has been determined by applying the subrenal capsule assay methodology to fresh surgical explants of the normal immunocompetent mice. The ability of emoxyl to inhibit growth of breast and colon tumours xenografts was determined. Emoxyl substitution for adriamycin in the combination therapy increases the therapeutic activity. The kinetic criterion .vkappa. calculated by the method of equivalent exponents was suggested to determine the tumour susceptibility to the drugs.
CC Anatomy and Histology, General and Comparative - Regeneration and Transplantation *11107
Pathology, General and Miscellaneous - Therapy *12512
Digestive System - Pathology *14006
Reproductive System - Pathology *16506
Pharmacology - General *22002
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Hominidae 86215
Muridae 86375
IT Miscellaneous Descriptors
HUMAN MOUSE EMOXYL ADRIAMYCIN ANTINEOPLASTIC-DRUG BREAST TUMOR COLON TUMOR
RN 1393-16-4D (LABELLED RUBROMYCIN)
84412-94-2 (EMOXYL)
23214-92-8Q, 25316-40-9Q (ADRIAMYCIN)

L164 ANSWER 42 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1988:312184 BIOSIS
DN BA86:29222
TI PHARMACOKINETICS OF A SPIN-LABELED RUBOMYCIN ANALOG.
AU KONOVALOVA N P; DIATCHKOVSKAYA R F; KUKUSHKINA G V; VOLKOVA L M; VARFOLOMEEV V N; DOMBROVSKY L S; SHAPIRO A B
CS INST. CHEM. PHYS., ACAD. SCI., USSR, 142432 MOSCOW, USSR.
SO NEOPLASMA (BRATISL), (1988) 35 (2), 185-190.
CODEN: NEOLA4. ISSN: 0028-2685.
FS BA; OLD
LA English
AB Pharmacokinetics of a spin-labeled analog of rubomycin (ruboxyl) was studied. Differences were found in ruboxyl pharmacokinetics in normal and tumor-bearing animals. Most of the drug was excreted within 6 h. The differences in pharmacokinetics of ruboxyl and nitroxyl radical were established.
CC Cytology and Cytochemistry - Animal *02506
Biochemical Studies - General 10060
Biophysics - Molecular Properties and Macromolecules 10506
Pathology, General and Miscellaneous - Therapy *12512
Metabolism - General Metabolism; Metabolic Pathways *13002
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Clinical Pharmacology 22005

Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Laboratory Animals - General 28002
BC Muridae 86375
IT Miscellaneous Descriptors
MOUSE RUBOXYL ANTINEOPLASTIC-DRUG NITROXYL RADICAL TUMOR-BEARING ANIMAL EXPERIMENTAL MODEL
RN 14332-28-6 (NITROXYL)
84412-94-2 (RUBOXYL)

L164 ANSWER 43 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1988:158679 BIOSIS
DN BA85:82332
TI USE OF FLUORESCENT DYES AS MOLECULAR PROBES FOR THE STUDY OF MULTIDRUG RESISTANCE.
AU NEYFAKH A A
CS INTERFACULTY LAB. MOLECULAR BIOL. BIOORGANIC CHEM., MOSCOW STATE UNIV., MOSCOW 119899, USSR.
SO EXP CELL RES, (1988) 174 (1), 168-176.
CODEN: ECREAL. ISSN: 0014-4827.
FS BA; OLD
LA English
AB Fluorescence microscopy has shown that 18 different fluorescent dyes, staining various intracelluar structures in transformed hamster fibroblasts (DM-15), did not stain or stained weakly multidrug-resistant cells selected from DM-15 by colchicine. Reduced staining by fluorescent dyes was characteristic also of five other tested multidrug-resistant cell lines of hamster and mouse origin, selected by actinomycin D, colcemid, rubomycin, and ruboxyl. Thé intensity of staining of two revertant cell lines was similar to that of parental sensitive cells. All tested inhibitors of multidrug resistance, including weak detergent, metabolic inhibitors, calcium channel blockers, calmodulin inhibitors, and reserpine, restored normal staining of multidrug-resistant cells. The dyes accumulated in resistant cells in presence of these inhibitors left the cells several minutes after the removal of the inhibitor from the incubation medium. Sensitive cells retained the dyes for several hours. The efflux of the dyes from resistant cells is an active process since it occurred even in the presence of the dyes in the incubation medium. The efflux could be blocked by all tested inhibitors of multidrug resistance and it is possibly a basic mechanism of the reduced staining of resistant cells. These data support the idea that multidrug resistance is based on active nonspecific efflux of the drugs and indicate that the simple procedure of cell staining can be used for the detection of resistant cells and further study of the phenomenon of multidrug resistance.
CC Microscopy Techniques - General and Special Techniques 01052
Microscopy Techniques - Cytology and Cytochemistry *01054
Cytology and Cytochemistry - Animal *02506
Comparative Biochemistry, General *10010
Biochemical Studies - General 10060
Movement 12100
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Neoplasms and Neoplastic Agents - Neoplastic Cell Lines *24005
Tissue Culture, Apparatus, Methods and Media 32500
BC Cricetidae 86310
Muridae 86375
IT Miscellaneous Descriptors
DM-15 HAMSTER FIBROBLASTS MOUSE NONSPECIFIC EFFLUX RESERPINE COLCHICINE ACTINOMYCIN D COLCEMID RUBOMYCIN RUBOXYL INCUBATION MEDIUM FLUORESCENCE MICROSCOPY
RN 50-55-5 (RESERPINE)
50-76-0 (ACTINOMYCIN D)
64-86-8 (COLCHICINE)
477-30-5 (COLCEMID)
11016-72-1 (RUBOMYCIN)
84412-94-2 (RUBOXYL)

L164 ANSWER 44 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1988:157517 BIOSIS
DN BA85:81170
TI CHARACTERIZATION OF ANTHRACYCLINE-RESISTANT STRAINS OF P388 LEUKEMIA.
AU GONCHAROVA S A; DEMIDOVA N S; SHIRYAEVA O A; SHEVTSOVA V N; KONOVALOVA N P
CS DIV., INST. CHEM. PHYS., ACAD SCI. USSR, CHERNOGOLOVKA, USSR.
SO EKSP ONKOL, (1987) 9 (4), 42-47.
CODEN: EKSODD. ISSN: 0204-3564.
FS BA; OLD
LA Russian
AB Two strains of P388 murine leukemia with acquired resistance to rubomycin (P388/rm) and its nitroxyl derivative ruboxyl (P388-rx). The rubomycin resistance has been developed by the 14th generation and ruboxyl one-by the 8th generation. The growth kinetic patterns and the cell cycle time of the parent and resistant strains were similar. An increased tumourogenicity of both resistant strains cells was found. The resistance development was accompanied by the appearance of the additional chromosome materials, namely of homogeneously staining region (P388/rx) and of double chromatin bodies (P388/rm). The partial recovery of sensitivity to rubomycin occurred during 36 generations (1 year). Simultaneously the genetic markers have been lost. The recovery of sensitivity to ruboxyl in this period was not observed. The obtained resistant strains possessed the multidrug resistance: the cross resistance of P388/rm and P388/rx to actinomycin D, Vinca alkaloids and colchicine was shown.
CC Cytology and Cytochemistry - Animal *02506
Biochemical Studies - General 10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Replication, Transcription, Translation *10300
Pathology, General and Miscellaneous - Therapy *12512
Blood, Blood-Forming Organs and Body Fluids - Blood, Lymphatic and Reticuloendothelial Pathologies *15006
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Pharmacology - General *22002
Pharmacology - Blood and Hematopoietic Agents *22008
Neoplasms and Neoplastic Agents - Pathology; Clinical Aspects; Systemic Effects *24004
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Neoplasms and Neoplastic Agents - Blood and Reticuloendothelial Neoplasms *24010
Developmental Biology - Embryology - Morphogenesis, General *25508
Tissue Culture, Apparatus, Methods and Media 32500
BC Muridae 86375
IT Miscellaneous Descriptors
MURINE LEUKEMIA CELLS RUBOMYCIN RUBOXYL ACTINOMYCIN D ANTINEOPLASTIC-DRUG GROWTH KINETIC PATTERNS CELL CYCLE TIME MULTI-DRUG RESISTANCE ANTI-LEUKEMIA THERAPY DRUG TESTING
RN 50-76-0 (ACTINOMYCIN D)
11016-72-1 (RUBOMYCIN)
84412-94-2 (RUBOXYL)

L164 ANSWER 45 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1987:59461 BIOSIS
DN BR32:29682
TI ANTHRACYCLINE RESPONSIVENESS OF HUMAN TUMORS AS FIRST TRANSPLANT GENERATION XENOGRAFTS IN THE NORMAL MOUSE.
AU DIATCHKOVSKAYA R F; VOLKOVA L M; KONOVALOVA N P
CS INST. OF CHEMICAL PHYSICS AND AC. OF SCI., CHERNOGOLOVKA, MOSCOW REGION, USSR.
SO UICC (UNION INTERNATIONALE CONTRE LE CANCER, INTERNATIONAL UNION AGAINST CANCER). 14TH INTERNATIONAL CANCER **CONGRESS**, BUDAPEST, HUNGARY, AUG. 21-27, 1986. ABSTRACTS, LECTURES, **SYMPOSIA** AND FREE COMMUNICATIONS, VOLS. 1, 2, 3, LATE ABSTRACTS, AND REGISTER. XVI+479P.(VOL. 1); XVI+298P.(VOL. 2); XVI+531P.(VOL. 3); 15P.(LATE

ABSTRACTS); 40P.(REGISTER) S. KARGER AG: BASEL, SWITZERLAND; NEW YORK, N.Y., USA; AKADEMIAI KIADO: BUDAPEST, HUNGARY. PAPER. (1986) 0 (0), 160. ISBN: 3-8055-4434-0 (KARGER), 963-05-4422-9 (VOL. 1), 963-05-4423-7 (VOL. 2), 963-05-4424-5 (VOL. 3), 963-05-4439-3 (LATE ABSTRACTS), 963-05-4425-3 (REGISTER), 963-05-4421-0 (GENERAL).

DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Studies - General 10060
Anatomy and Histology, General and Comparative - Experimental Anatomy *11104
Pathology, General and Miscellaneous - Therapy 12512
Pharmacology - Clinical Pharmacology 22005
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
BC Hominidae 86215
Muridae 86375
IT Miscellaneous Descriptors
ABSTRACT ADRIAMYCIN ACLACINOMYCIN RUBOXYL ANTINEOPLASTIC-DRUG
RN 66676-88-8 (ACLACINOMYCIN)
84412-94-2 (RUBOXYL)
23214-92-8Q, 25316-40-9Q (ADRIAMYCIN)

L164 ANSWER 46 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1985:244081 BIOSIS
DN BA79:24077
TI EFFECT OF RUBOMYCIN AND ITS PARAMAGNETIC ANALOG ON DNA SYNTHESIS.
AU DEDERER L YU; GORBACHEVA L B
CS INST. CHEM. PHYS., ACAD. SCI. USSR, MOSCOW, USSR.
SO ANTIBIOTIKI (MOSC), (1984) 29 (6), 442-445.
CODEN: ANTBAL. ISSN: 0003-5637.
FS BA; OLD
LA Russian
AB Ruboxyl, a paramagnetic analog of rubomycin, was synthesized and subjected to a preliminary investigation at the Institute of Chemical Physics of the Academy of Sciences of the USSR. The drug is characterized by a higher antitumor activity, broader spectrum and lower general and cardiac toxicity. This is the first attempt of comparative biochemical investigation of rubomycin, ruboxyl and the nitroxyl radical at the level of DNA replication. The effect of these drugs on the synthesis of DNA in the cells of leukemia P-388, the bone marrow and heart of mice was studied. The degree and duration of the DNA synthesis inhibition in the tumor cells correlated well with the antitumor activity of the drugs. On the 3rd day after administration, rubomycin and ruboxyl induced stimulation of the DNA synthesis in the cells of the bone marrow. This might be explained by transfer of a part of the population of the bone marrow cells from G0 phase due to the cytotoxic damages of the proliferating cells. The DNA synthesis stimulation in the bone marrow was most likely associated with the toxic effect of the drugs. No correlation between the cardiotoxicity and inhibition of the DNA synthesis in the heart cells of the mice was observed. The nitroxyl radical showed no biological activity in this model. The average lifespan of the mice treated with the nitroxyl radical was the same as that of the control animals. A decrease in the incorporation of 2-14C-thymidine into DNA of the tumor, bone marrow and heart was observed in the tumor carriers with development of the tumor.
CC Cytology and Cytochemistry - Animal 02506
Radiation - Radiation and Isotope Techniques 06504
Comparative Biochemistry, General *10010
Biochemical Studies - General *10060
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Replication, Transcription, Translation *10300
Biophysics - Molecular Properties and Macromolecules 10506
Metabolism - Nucleic Acids, Purines and Pyrimidines *13014

Cardiovascular System - Heart Pathology 14506
Blood, Blood-Forming Organs and Body Fluids - Blood, Lymphatic and Reticuloendothelial Pathologies 15006
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System 15008
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology 18006
Pharmacology - General *22002
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Immunological Processes and Allergy 22018
Toxicology - Pharmacological Toxicology *22504
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Neoplasms and Neoplastic Agents - Blood and Reticuloendothelial Neoplasms 24010
BC Muridae 86375
IT Miscellaneous Descriptors
LEUKEMIA P-388 MOUSE RUBOXYL NITROXYL RADICAL ANTINEOPLASTIC-DRUG TOXICITY BONE MARROW HEART
RN 11016-72-1 (RUBOMYCIN)
14332-28-6 (NITROXYL)
84412-94-2 (RUBOXYL)

L164 ANSWER 47 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1984:220224 BIOSIS
DN BA77:53208
TI NITROXYL DERIVATIVES OF RUBOMYCIN.
AU EMANUEL' N M; KONOVALOVA N P; D'YACHKOVSKAYA R F; DENISOVA L K
CS BRANCH INST. CHEM. PHYS., ACAD. SCI. USSR, CHERNOGOLOVKA, USSR.
SO ANTIBIOTIKI (MOSC), (**1982 (RECD 1983)**) 27 (11), 811-815.
CODEN: ANTBAL. ISSN: 0003-5637.
FS BA; OLD
LA Russian
AB The toxic and antitumor effects of new analogs of rubomycin were studied. Studies with mice showed that spin-labeled derivatives had the lowest toxicity and highest antitumor activity. The diamagnetic analog was similar to rubomycin in its antitumor effect. Ruboxyl-1 had a lower cardiotoxicity than rubomycin and did inhibit hemopoiesis at the maximum tolerated doses.
CC Cytology and Cytochemistry - Animal 02506
Comparative Biochemistry, General 10010
Biochemical Studies - General 10060
Biochemical Studies - Carbohydrates 10068
Biophysics - Molecular Properties and Macromolecules 10506
Cardiovascular System - Heart Pathology *14506
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies 15004
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System 15008
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Toxicology - Pharmacological Toxicology *22504
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Chemotherapy - General; Methods; Metabolism *38502
BC Muridae 86375
IT Miscellaneous Descriptors
MOUSE RUBOXYL 1 ANTINEOPLASTIC-DRUG CARDIO TOXICITY HEMOPOIESIS INHIBITION
RN 11016-72-1D (RUBOMYCIN)
14332-28-6D (NITROXYL)
84412-94-2 (RUBOXYL 1)

L164 ANSWER 48 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1983:284108 BIOSIS
DN BA76:41600
TI MONO CLONAL ANTIBODIES TO A NITROXIDE LIPID HAPTEN.
AU BALAKRISHNAN K; HSU F J; HAFEMAN D G; MCCONNELL H M
CS STAUFFER LAB. PHYSICAL CHEMISTRY, STANFORD UNIV., STANFORD, CA 94305.

SO BIOCHIM BIOPHYS ACTA, (1982) 721 (1), 30-38.
CODEN: BBACAQ. ISSN: 0006-3002.
FS BA; OLD
LA English
AB The isolation and characterization of a [mouse] hybridoma cell line [from the fusion of plasmacytoma NS-1 and SP2/0 cells with spleen cells] producing a monoclonal IgG1 antibody against a spin-label nitroxide group is described. The antibody recognizes a synthetic hapten containing linked dinitrophenyl and 2,2,6,6-tetramethylpiperidinyl 1-oxy groups, having an affinity of 3.6 .+-. 1.0 .cntdot. 106 M-1 for the soluble hapten at 25.degree. C. The antibody binds to phospholipid vesicles containing 2 mol% of spin label-derivitized lipid (lipid hapten) with an affinity of 1.5 .+-. 0.2 .cntdot. 108 M-1. This monoclonal IgG1 mediates the binding of hapten-bearing lipid vesicles to mouse macrophage RAW264 cells bearing Fc receptors. The cellular responses to this binding are similar to those observed previously using polyclonal rabbit anti-hapten IgG. As with the heterogeneous antibodies, the monoclonal IgG1 is more efficient in mediating cellular uptake when the vesicles are in the fluid physical state (dimyristoylphosphatidylcholine at 37.degree. C) compared to solid (dipalmitoylphosphatidylcholine at 37.degree. C). Despite the enhanced binding of fluid phospholipid vesicles to cells, only the solid vesicles triggered a significant respiratory burst in RAW264 macrophages.
CC Biochemical Studies - General 10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Lipids 10066
Biochemical Studies - Carbohydrates 10068
Biophysics - Molecular Properties and Macromolecules *10506
Metabolism - Carbohydrates *13004
Metabolism - Proteins, Peptides and Amino Acids *13012
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
Blood, Blood-Forming Organs and Body Fluids - Blood, Lymphatic and Reticuloendothelial Pathologies 15006
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Neoplasms and Neoplastic Agents - Neoplastic Cell Lines 24005
Neoplasms and Neoplastic Agents - Blood and Reticuloendothelial Neoplasms 24010
Tissue Culture, Apparatus, Methods and Media 32500
Immunology and Immunochemistry - General; Methods *34502
BC Muridae 86375
IT Miscellaneous Descriptors
MOUSE PLASMA CYTOMA NS-1 CELLS SP-2-0 CELLS NEOPLASTIC MACROPHAGE RAW-264 CELLS MOUSE SPLEEN CELL DI NITRO PHENYL 2 2 6 6 TETRA METHYL PIPERIDINYL-1-OXY GROUP IMMUNO GLOBULIN G-1 FC RECEPTOR
RN **2564-83-2** (2 2 6 6 TETRA METHYL PIPERIDINYL-1-OXY)
13408-29-2 (NITROXIDE)

L164 ANSWER 49 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1981:243530 BIOSIS
DN BA72:28514
TI FORMATION OF 11-TRANS SLOW REACTING SUBSTANCES.
AU ATRACHE V; SOK D-E; PAI J-K; SIH C J
CS SCH. OF PHARMACY, UNIVERSITY OF WISCONSIN, MADISON, WISCONSIN 53706.
SO PROC NATL ACAD SCI U S A, (1981) 78 (3), 1523-1526.
CODEN: PNASA6. ISSN: 0027-8424.
FS BA; OLD
LA English
AB Under strongly basic conditions [excess LiOH, dimethoxyethane/water (4:1, vol/vol)], purified slow reacting substances (SRS) SRS-GSH and SRS-Cys were not isomerized to their corresponding 11-trans isomers. Addition of thiols such as glutathione (GSH) or L-cysteine to this basic medium produced various amounts of 11-trans-SRS, depending on the thiol concentration. This chemical isomerization was inhibited by the radical scavenger 4-hydroxy-2,2,6,6-tetramethylpiperidinooxy free radical (HTMP); the inhibition suggests that the thiyl radical is added reversibly to the triene system at C-12, resulting in the overall cis .fwdarw. trans

isomerization of the 11,12 double bond. Because the amount of 11-trans-SRS-Cys produced by intact RBL-1 cells apparently contain enzymes systems that form peroxides, which enhance the formation of thiyl radicals, required for cis .fwdarw. trans isomerization. HTMP inhibited the formation of 11-trans-SRS-Cys in this cell system.

CC Cytology and Cytochemistry - Animal 02506
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Lipids 10066
Biophysics - Molecular Properties and Macromolecules 10506
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease 12508
Metabolism - Lipids *13006
Metabolism - Proteins, Peptides and Amino Acids *13012
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
Blood, Blood-Forming Organs and Body Fluids - Blood, Lymphatic and Reticuloendothelial Pathologies *15006
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Immunological Processes and Allergy *22018
Neoplasms and Neoplastic Agents - Neoplastic Cell Lines 24005
Neoplasms and Neoplastic Agents - Blood and Reticuloendothelial Neoplasms *24010
Immunology and Immunochemistry - General; Methods *34502
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
Allergy *35500

BC Muridae 86375

IT Miscellaneous Descriptors
RAT BASOPHILIC LEUKEMIA CELL 4 HYDROXY-2 2 6 6-TETRAMETHYLPIPERIDINOOXY FREE RADICAL METABOLIC-DRUG IMMUNOLOGIC-DRUG GLUTATHIONE L CYSTEINE

RN 52-90-4 (L CYSTEINE)
70-18-8 (GLUTATHIONE)
2226-96-2 (4 HYDROXY-2 2 6 6-TETRAMETHYLPIPERIDINOOXY)

L164 ANSWER 50 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1980:280287 BIOSIS
DN BA70:72783
TI MODIFICATION OF THE ACTION OF MISONIDAZOLE 1. EFFECT OF TRI ACETONEAMINE N OXYL ON TOXICITY.
AU SKOV K A; PALCIC B; HARRISON I E; SKARSGARD L D
CS MED. BIOPHYS. UNIT, B.C. CANCER RES. CENT., 601 W. 10TH AVE., VANCOUVER, B.C. V5Z 1L3, CAN.
SO INT J RADIAT BIOL RELAT STUD PHYS CHEM MED, (1980) 37 (6), 601-612. CODEN: IJRBA3. ISSN: 0020-7616.
FS BA; OLD
LA English
AB The toxicity of misonidazole, an electron affinic radiosensitizer, is greatly reduced by TAN [triacetoneamine-N-oxyl], a free radical radiosensitizer. The production of single-strand breaks in DNA of mammalian cells [hamster], incubated in dilute suspension with misonidazole (15 mM) under hypoxic conditions is greatly decreased by the presence of TAN (10 mM). The survival of cells is greatly enhanced if TAN is present at a concentration of 10 mM and even less. The use as a potential adjunct for the radiotherapeutic treatment of tumors and possible mechanisms are discussed.

CC Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - Animal *03506
Radiation - Radiation and Isotope Techniques 06504
Radiation - Radiation Effects and Protective Measures *06506
Biochemistry - Gases *10012
Biochemical Studies - General 10060
Pathology, General and Miscellaneous - Necrosis 12510
Pathology, General and Miscellaneous - Therapy 12512
Metabolism - Energy and Respiratory Metabolism *13003
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003

Toxicology - Pharmacological Toxicology *22504
Toxicology - Antidotes and Preventative Toxicology *22505
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Chemotherapy - General; Methods; Metabolism *38502
BC Mammalia - Unspecified 85700
Cricetidae 86310
IT Miscellaneous Descriptors
HAMSTER MAMMAL RADIOSENSITIZER PHARMACEUTICAL-ADJUNCT TUMOR RADIO THERAPY HYPOXIA
RN **2896-70-0** (TRI ACETONEAMINE N OXYL)
13551-87-6 (MISONIDAZOLE)

L164 ANSWER 51 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1980:89213 BIOSIS
DN BR19:26711
TI QUANTITATIVE INVESTIGATION WITH EPR OF 2 2 6 6 TETRA METHYL-4-OXO PIPERIDINE-1-OXYL IN HOMOGENATES FROM TISSUES OF HAMSTERS WITH TRANSPLANTED MELANOTIC MALIGNANT MELANOMA.
AU RAIKOV Z D; BLAGOEVA P M; YORDANOV N D
CS DEP. BIOCHEM., INST. ONCOL., BULG. ACAD. SCI., SOFIA 1156, BULG.
SO KLAUS, S. N. (ED.). PIGMENT CELL, VOL. 5. PATHOPHYSIOLOGY OF MELANOCYTES; **PROCEEDINGS** OF THE 10TH INTERNATIONAL PIGMENT CELL **CONFERENCE**, CAMBRIDGE, MASS., USA, OCT. 8-12, 1977 (PART 2). XVI+317P. S. KARGER: BASEL, SWITZERLAND; NEW YORK, N.Y., USA. ILLUS. (**1979 (RECD 1980)**) 0 (0), P210-212.
CODEN: PGTCA4. ISSN: 0301-0139. ISBN: 3-8055-2973-2.
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Methods - General 10050
Biochemical Studies - General 10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biophysics - General Biophysical Techniques 10504
Metabolism - General Metabolism; Metabolic Pathways *13002
Metabolism - Proteins, Peptides and Amino Acids *13012
Neoplasms and Neoplastic Agents - Biochemistry *24006
BC Cricetidae 86310
IT Miscellaneous Descriptors
MELANIN PRODUCTION
RN **2896-70-0** (2 2 6 6 TETRA METHYL-4-OXO PIPERIDINE-1-OXYL)

L164 ANSWER 52 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1977:108492 BIOSIS
DN BA63:3356
TI SYNTHESIS AND ESR STUDY OF SPIN LABELED COMPOUNDS RELATED TO TUMOR GROWTH INHIBITORY NITROARYL AZIRIDINES.
AU DODD N J F; HARCUS R G; PRESTON P N
SO Z NATURFORSCH SECT C BIOSCI, (1976) 31 (5-6), 328-330.
CODEN: ZNFCAP. ISSN: 0341-0471.
FS BA; OLD
LA Unavailable
AB Three stable free radicals were prepared which are akin to 5-aziridino-2,4-dinitrobenzamide (CB 1954). These compounds contain a nitroxide function. The metabolism and excretion of 2 such compounds in mice was monitored by ESR spectroscopy and compared with that of the simpler nitroxide, 4-keto-2,2,6,6-tetramethylpiperidino-1-oxyl (tempone).
CC Clinical Biochemistry; General Methods and Applications 10006
Comparative Biochemistry, General 10010
Biochemical Methods - General 10050
Biochemical Studies - General *10060
Biophysics - General Biophysical Techniques 10504
Biophysics - Molecular Properties and Macromolecules *10506
Pathology, General and Miscellaneous - Therapy 12512
Metabolism - General Metabolism; Metabolic Pathways *13002

Urinary System and External Secretions - Physiology and Biochemistry 15504
Pharmacology - General *22002
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Chemotherapy - General; Methods; Metabolism *38502
BC Muridae 86375
IT Miscellaneous Descriptors
MOUSE TEMPONE 5 AZIRIDINO-2 4-DINITRO BENZAMIDE CB-1954 ANTI NEOPLASTIC-DRUGS DRUG METABOLISM
RN **2896-70-0** (TEMPONE)
21919-05-1 (5 AZIRIDINO-2 4-DINITRO BENZAMIDE)
21919-05-1 (CB-1954)

L164 ANSWER 53 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1975:237581 BIOSIS
DN BA60:67577
TI CARCINOGENICITY OF METHYLATED NITROSO PIPERIDINES.
AU LIJINSKY W; TAYLOR H W
SO INT J CANCER, (1975) 16 (2), 318-322.
CODEN: IJCNAW. ISSN: 0020-7136.
FS BA; OLD
LA Unavailable
CC Cytology and Cytochemistry - Animal 02506
Biochemistry - Physiological Water Studies 10011
Biochemical Studies - General 10060
Biophysics - Molecular Properties and Macromolecules 10506
Pathology, General and Miscellaneous - Necrosis 12510
Digestive System - Pathology *14006
Respiratory System - Pathology *16006
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Dental and Oral Biology - General; Methods 19001
Routes of Immunization, Infection and Therapy 22100
Toxicology - General; Methods and Experimental *22501
Neoplasms and Neoplastic Agents - Carcinogens and Carcinogenesis *24007
BC Muridae 86375
IT Miscellaneous Descriptors
RAT 2 METHYLNITROSO PIPERIDINE 3 METHYLNITROSO PIPERIDINE 4 METHYLNITROSO PIPERIDINE 2 6 DI METHYLNITROSO PIPERIDINE 2 2 6 6 TETRA METHYLNITROSO PIPERIDINE CARCINOGENS NASAL TURBINATE UPPER GASTRO INTESTINAL TUMORS HEPATO CELLULAR CARCINOMA
RN 110-89-4 (PIPERIDINE)
110-89-4D (PIPERIDINES)
6130-93-4 (2 2 6 6 TETRA METHYLNITROSO PIPERIDINE)
7247-89-4 (2 METHYLNITROSO PIPERIDINE)
17721-95-8 (2 6 DI METHYLNITROSO PIPERIDINE)
110-89-4 (PIPERIDINE)
110-89-4D (PIPERIDINES)
6130-93-4 (2 2 6 6 TETRA METHYLNITROSO PIPERIDINE)
7247-89-4 (2 METHYLNITROSO PIPERIDINE)
17721-95-8 (2 6 DI METHYLNITROSO PIPERIDINE)

L164 ANSWER 54 OF 54 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1974:209892 BIOSIS
DN BA58:39586
TI CHANGE IN THE EFFECTIVENESS OF RADIATION BY MEANS OF FREE IMINOXYL RADICALS.
AU VORONINA S S; GRIGORYAN G L; PELEVINA I I
SO IZV AKAD NAUK SSSR SER BIOL, (1972) (5), 723-730.
CODEN: IANBAM. ISSN: 0002-3329.
FS BA; OLD
LA Unavailable
CC Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - Animal *03506

Radiation - Radiation and Isotope Techniques *06504
Radiation - Radiation Effects and Protective Measures *06506
Biochemical Studies - General 10060
Biophysics - Molecular Properties and Macromolecules 10506
Pathology, General and Miscellaneous - Therapy 12512
Metabolism - General Metabolism; Metabolic Pathways 13002
Blood, Blood-Forming Organs and Body Fluids - Blood, Lymphatic and Reticuloendothelial Pathologies *15006
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System 15008
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology 18006
Pharmacology - Drug Metabolism; Metabolic Stimulators 22003
Pharmacology - Blood and Hematopoietic Agents *22008
Pharmacology - Connective Tissue, Bone and Collagen - Acting Drugs 22012
Neoplasms and Neoplastic Agents - Neoplastic Cell Lines *24005
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Neoplasms and Neoplastic Agents - Blood and Reticuloendothelial Neoplasms *24010
Tissue Culture, Apparatus, Methods and Media 32500
Chemotherapy - General; Methods; Metabolism *38502
BC Muridae 86375
IT Miscellaneous Descriptors
MOUSE NKLY ASCITES LYMPHO SARCOMA CELLS 2 2 6 6 TETRA METHYL-4-OXO PIPERIDINE 1 OXYL ANTI NEOPLASTIC-DRUG CHROMOSOME ABERRATIONS
RN **2896-70-0** (2 2 6 6 TETRA METHYL-4-OXO PIPERIDINE 1 OXYL)
13408-29-2 (IMINOXYL)

=> fil cancer

FILE 'CANCERLIT' ENTERED AT 11:46:46 ON 28 OCT 2000

FILE COVERS 1963 TO 12 Oct 2000 (20001012/ED)

CANCERLIT has been reloaded to reflect the annual MeSH changes made by the National Library of Medicine for 2000. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d his l165-

(FILE 'BIOSIS' ENTERED AT 11:44:15 ON 28 OCT 2000)

FILE 'CANCERLIT' ENTERED AT 11:44:47 ON 28 OCT 2000
L165 90 S L154
L166 338 S L105,L106,L110,L165
L167 75 S L166 NOT MEDLINE/OS
L168 74 S L167 AND PY<=1997
L169 7 S L168 AND TEMPOL
L170 67 S L168 NOT L169
L171 0 S L1,L2 AND L170
L172 0 S L104 AND L170

FILE 'CANCERLIT' ENTERED AT 11:46:46 ON 28 OCT 2000

=> d all tot l169

L169 ANSWER 1 OF 7 CANCERLIT
AN 1998638298 CANCERLIT
DN 98638298
TI DNA damage and apoptosis in human leukemic cells treated with the piperidine **nitroxide TEMPOL** (Meeting abstract).

AU Monti E; Gariboldi M B; Supino R; Piccinini F
CS Inst. of Pharmacology, Univ. of Milan, Italy.
SO Proc Annu Meet Am Assoc Cancer Res, **(1997)**. Vol. 38, pp. A1298.
ISSN: 0197-016X.
DT (MEETING ABSTRACTS)
FS ICDB
LA English
EM 199806
AB Piperidine **nitroxide** radicals act as antioxidants in several free radical-mediated pathologies (Krishna and Samuni, Methods Enzymol 234:580, 1994). A recent study showed that these compounds are mutagenic as well as cytotoxic against DNA repair-deficient bacterial strains (Wang et al, Biochim Biophys Acta 1305:71, 1996). This observation suggested that similar effects might be elicited in tumor cell lines. In the present study we evaluated the cytotoxicity of 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl (**TEMPOL**) against two human leukemic cell lines, HL-60 and KG1. Our results show that HL-60 cells are more sensitive than KG1 (IC50 0.35 +/- 0.08 mM and 1.3 +/- 0.14 mM, respectively for 96-h exposure, M +/- SE). Analysis of DNA fragmentation by agarose gel electrophoresis and filter binding assay in **TEMPOL** -treated HL-60 cells showed a dose-dependent effect, which was absent in KG1 cells. The two cell lines exhibited different cell cycle distributions following **TEMPOL** treatment, with a partial G1 block for KG1 and a shift towards S and G2/M phases for HL-60. Cell cycle studies also evidenced a dose and time-dependent increase of apoptosis for HL-60 but not for KG1 cells. Immunoblot analysis of bcl-2 indicated the presence of higher protein levels in KG1 than in HL-60 cells. We conclude that cytotoxic effect of **TEMPOL** in human leukemic cells is related to induction of apoptosis.
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**
CN 0 (Cyclic N-Oxides)

L169 ANSWER 2 OF 7 CANCERLIT
AN 97616241 CANCERLIT
DN 97616241
TI Protection against Adriamycin cytotoxicity and inhibition of DNA topoisomerase II activity by 3,4-dihydroxybenzoic acid (Meeting abstract).
AU DeGraff W G; Myers L S; Mitchell J B; Hahn S M
CS Radiation Biology Branch, NCI, Bethesda, MD 20892.
SO Proc Annu Meet Am Assoc Cancer Res, **(1997)**. Vol. 38, pp. A148.
ISSN: 0197-016X.
DT (MEETING ABSTRACTS)
FS ICDB
LA English
EM 199708
AB Adriamycin is thought to cause toxicity through intercalation into DNA, stabilization of topoisomerase II-DNA complexes or production of free radicals by redox cycling of the semiquinone. We have previously shown that **Tempol** a stable **nitroxide** free radical can protect against cytotoxicity induced by agents that produce reactive oxygen species, and that **Tempol** does not protect against Adriamycin-induced cytotoxicity or DNA damage. The benzoic acid derivative 3,4-dihydroxybenzoic acid (DHB) was investigated for its ability to protect against Adriamycin-induced cytotoxicity and DNA double strand breaks. V79 cells were treated with Adriamycin or its non-redox cycling analog immunodaunorubicin in the presence or absence of mM concentrations of DHB. DHB provided significant protection with a dose modifying factor greater than 25 for Adriamycin and nearly 2 for immunodaunorubicin. DHB also caused a dose-dependent decrease in DNA double strand breaks as measured by pulsed field gel electrophoresis. Assays of topoisomerase II activity show that DHB inhibits topoisomerase II in a dose-dependent manner. These data identify DHB asa non-toxic inhibitor of DNA topoisomerase II and suggest that much of the cytotoxicity of Adriamycin is due to mechanisms other than redox cycling by the semiquinone
RN 99-50-3 (protocatechuic acid); 23214-92-8 (Doxorubicin)
CN 0 (Anticarcinogenic Agents); 0 (Antineoplastic Agents); EC 5.99.1.3 (DNA

Topoisomerase (ATP-Hydrolysing)); 0 (Hydroxybenzoic Acids)

L169 ANSWER 3 OF 7 CANCERLIT
AN 96625346 CANCERLIT
DN 96625346
TI Genotoxic studies of 2-methoxyethanol, 2-butoxyethanol and their aldehyde metabolites by cytogenetic and molecular mutagenic assays.
AU Chiewchanwit T
CS Univ. of Texas Grad. Sch. of Biomed. Sci. at Galveston.
SO Diss Abstr Int [B], **(1995)**. Vol. 56, No. 4, pp. 1973.
ISSN: 0419-4217.
DT (THESIS)
FS ICDB
LA English
EM 199606
AB Glycol ethers, such as 2-methoxyethanol (2-ME) and 2-butoxyethanol (2-BE), are used extensively as solvents. Most glycol ethers can induce reproductive and hematopoietic toxicities; however, their genotoxicity is still unclear. A previous study from our laboratory indicated that methoxyacetaldehyde (MALD, a metabolite of 2-ME) is mutagenic, while 2-ME and methoxyacetic acid (the subsequent metabolite) are not. MALD induces gpt gene mutations in CHO-AS52 but not hprt gene mutations in CHO-K1-BH4 cells. We hypothesized that MALD could induce large deletion mutations in both CHO cell lines and that only mutated AS52 cells would survive. To test the hypothesis, we examined the induction of deletion mutations by MALD in CHO-AS52 mutants and of chromosome aberrations in both CHO cell lines. Using a nested-polymerase chain reaction assay, a 2.3 fold greater frequency of deleted gpt gene was seen in MALD-induced (as compared to spontaneous) mutants, while ethylnitrosourea-induced mutants (negative control for multilocus deletion) had a 0.2 fold lower frequency of deleted gpt genes than did spontaneous mutants. MALD induced a significant and dose-dependent increase in chromosome aberrations in both CHO cell lines (p less than 0.05). These data support the hypothesis that MALD induces large deletion mutations. To explore the mechanism of action, **TEMPOL** and catalase, which are reactive oxygen species (ROS) modulators, were used to examine whether the formation of ROS might be involved. No protection from MALD-induced chromosome damage was found after pre- and co-treatment with either **TEMPOL** or catalase, indicating that the generation of ROS may not be the primary mechanism of action of MALD. Since aldehydes have been reported to induce crosslinks, this may be the mechanism of action of MALD. In comparison with 2-ME, 2-BE is more cytotoxic, while MALD is more toxic than 2-butoxyacetaldehyde (BALD). Moreover, MALD is mutagenic, while BALD is not. Our data are consistent with the general observation that cytotoxicity increases with increased chain length of the alkyl group of glycol ethers, whereas mutagenicity decreases with increased chain length of the alkyl group of aldehydes. (Full text available from University Microfilms International, Ann Arbor, MI, as Order No. AADAA-I9527003)

L169 ANSWER 4 OF 7 CANCERLIT
AN 96605167 CANCERLIT
DN 96605167
TI Molecular analysis of bleomycin-induced mutations at the hprt and gpt loci in Chinese hamster ovary cells.
AU An J
CS Univ. of Texas Grad. Sch. of Biomed. Sci. at Galveston.
SO Diss Abstr Int [B], **(1995)**. Vol. 55, No. 9, pp. 3795.
ISSN: 0419-4217.
DT (THESIS)
FS ICDB
LA English
EM 199605
AB The bleomycin (BLM)-induced mutations were analyzed at the hypoxanthine-guanine phosphoribosyltransferase (hprt) and the xanthine-guanine phosphoribosyl-transferase (gpt) loci in Chinese hamster ovary (CHO) cell clones K1-BH4 and AS52, respectively. To reveal the role

of reactive oxygen species (ROS) in BLM mutagenesis, TRIEN (triethylenetetramine, a superoxide dismutase (SOD) inhibitor) and **TEMPOL** (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl, an SOD mimic) were used. The cytotoxicity and mutagenicity of BLM, and BLM with TRIEN or **TEMPOL** pretreatment were determined by the CHO/HPRT and AS52/GPT mutation assays. TRIEN pretreatment significantly increased the cytotoxicity and mutagenicity of BLM and **TEMPOL** pretreatment significantly decreased the mutagenicity of BLM in both cell types. The mutation spectra were analyzed by a polymerase chain reaction-based comprehensive procedure. Among 54 HPRT- mutants induced by BLM, 44.4% had large deletions, 7.4% had base substitutions, 20.4% had small deletions or insertions, 7.4% had abnormal cDNAs, and 20.4% had no cDNAs. Among 28 HPRT- mutants induced by BLM after TRIEN pretreatment, 39.3% had large deletions, 14.3% had base substitutions, 28.6% had small deletions or insertions, 10.7% had abnormal cDNAs, and 7.1% had no cDNAs. Among 30 HPRT- mutants induced by BLM after **TEMPOL** pretreatment, 50% had large deletions, 16.7% had base substitutions, 16.7% had small deletions or insertions, 6.7% had abnormal cDNAs, and 10% had no cDNAs. Among 59 GPT- mutants induced by BLM, 61% had large deletions, 11.9% had base substitutions, and 23.7% had small deletions or insertions, and 3.4% had the possible gene rearrangements. Among 37 GPT- mutants induced by BLM after TRIEN pretreatment, 56.8% had large deletions, 13.5% had base substitutions, and 29.7% had small deletions or insertions. Among 44 GPT- mutants induced by BLM after **TEMPOL** pretreatment, 61.4% had large deletions, 9.1% had base substitutions, 27.3% had small deletions or insertions, and 2.3% had no detectable changes in the gene. These data suggested that TRIEN caused a shift from a ROS-mediated (via BLM) mutation spectrum to a spontaneous mutation spectrum. The results of this study support the hypothesis that hydroxyl radical is one of the ROS causing deletion mutations mediated by BLM. (Full text available from University Microfilms International, Ann Arbor, MI, as Order No. AAD95-03692)

RN 11056-06-7 (Bleomycin)

CN EC 2.4.2.22 (xanthine phosphoribosyltransferase); 0 (DNA, Complementary); EC 2.4.2.8 (Hypoxanthine Phosphoribosyltransferase); 0 (Mutagens); EC 2.4.2. (Pentosyltransferases); 0 (Reactive Oxygen Species)

L169 ANSWER 5 OF 7 CANCERLIT

AN 95610079 CANCERLIT

DN 95610079

TI Cytotoxicity of **tempol**, a piperidine **nitroxide** spin label, against different neoplastic and non-neoplastic cell lines (Meeting abstract).

AU Monti E; Gariboldi M; Supino R; Piccinini F

CS Inst. of Pharmacology, Univ. of Milan, Milan, Italy.

SO Proc Annu Meet Am Assoc Cancer Res, **(1995)**. Vol. 36, pp. A2304. ISSN: 0197-016X.

DT (MEETING ABSTRACTS)

FS ICDB

LA English

EM 199508

AB The stable **nitroxide tempol** (4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl) is widely used as a probe in biophysical studies and was recently reported to act as radioprotector in mice. The possible cytotoxic effects of **Tempol** were tested on a panel of human and rodent cell lines, including human breast (MCF-7/WT, MCF7/ADRR and MDA-231) and ovarian (OVCAR-3) carcinoma cells, Chinese hamster ovary (CHO) cells, rat hepatocytes (BRL 3A) and rat hepatoma (MH1C1) cells. Interestingly, and in contrast with the parent non-hydroxylated compound **TEMPO** and its 4-amino-derivative tempamine, **tempol** was found to be significantly more cytotoxic against neoplastic than against non-neoplastic cell lines, with the following IC50 values (mM) in a 4-day MTT assay: 0.208 (MCF-7/WT), 0.222 (OVCAR-3), 0.410 (MCF-7/ADRR), 0.571 (MDA-231), 0.773 (MH1C1), 0.891 (CHO) and 1.073 (BRL 3A). Cellular pharmacokinetic data obtained in MCF-7/WT cells suggest that the hydroxylamine metabolite of **tempol** is involved in its cytotoxic effects. Cell cycle studies indicate that cell death does not occur by

apoptosis and that cell cycle effects are not prominent in the cytotoxicity of **tempol**.
RN **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**
CN 0 (Antineoplastic Agents); 0 (Cyclic N-Oxides); 0 (Radiation-Protective Agents)

L169 ANSWER 6 OF 7 CANCERLIT
AN 94699777 CANCERLIT
DN 94699777
TI Potential use of **nitroxides** in radiation oncology (Meeting abstract).
AU Mitchell J B; Krishna M C; Hahn S; Liebmann J; Cook J A; DeGraff W; Cuscela D; Sullivan F; Johnstone P; Gamson J; et al
CS Radiation Biology Section, Radiation Oncology Branch, NCI, Bethesda, MD.
SO Non-serial, **(1993)**. Anticarcinogenesis and Radiation Protection, 4th International Conference:Mechanisms, Biomarkers, Molecular Diagnostics and Preventive Strategies. April 18-23, 1993, Baltimore, Maryland.
DT Journal; Article; (JOURNAL ARTICLE)
FS ICDB
LA English
EM 199411
AB There is a continued need to improve the effectiveness of radiation treatment of human malignancies. We have recently identified a new class of non-thiol radioprotectors that may have utility in clinical radiotherapy. **Nitroxides** which have already found considerable utility both in ESR and NMR spectroscopy, were recently shown to exhibit superoxide dismutase mimetic activity and were capable of protecting mammalian cells against superoxide and hydrogen peroxide cytotoxicity. Since ionizing radiation in an oxygen environment produces superoxide, hydrogen peroxide, and hydroxyl radical, we anticipated that **nitroxides** might also provide protection against radiation. In vitro aerobic radiation survival studies using Chinese hamster cells pretreated with both 5- and 6-membered ring **nitroxides** revealed radiation protection factors which ranged from 1.2 to 2.4 at a concentration of 10 mM. Protection was observed only for the oxidized form of **nitroxide**-reduced forms (hydroxylamines) were not protective. Interestingly, one **nitroxide** (**tempol**) was shown to sensitize hypoxic cells to radiation. In mice, the maximally tolerated dose of **tempol** (275 mg/kg) given 10 min before whole body irradiation gave a 1.3 protection factor at the LD 50/30. Preliminary studies have also been initiated to determine if **tempol** protects tumor in addition to normal tissues. TCD50 studies of the murine RIF tumor in the presence or absence of **tempol** has shown no protection. Thus, our preliminary studies establish **nitroxides** as potential candidates for normal tissue protection in the clinic. Of course additional work and a more complete survey of different **nitroxides** to identify the most effective agent will be required before these agents will be considered for the clinic. Studies have also been initiated to determine if the combination of **tempol** with the hematopoietic growth factor stem cell factor (SCF, c-kit ligand) would provide enhanced radiation protection in mice compared with the protection afforded by either agent alone. Treatment of mice pre- and post-radiation with SCF alone (100 ug/kg at -20, -4, and +4 hr) provided protection (76%) at 10 Gy and only 4% at 11 Gy. **Tempol** given 10 min prior to radiation protected (55%) mice from radiation doses up to 9 Gy. The combination of SCF and TP increased survival to 32% compared with only 2% survival with either agent alone (p less than 0.01) at 11 Gy. Thus, the combination of SCF and **tempol** may prove beneficial toward protecting normal tissues. Lastly, topical application of **tempol** has been shown to protect against radiation-induced alopecia (guinea pig model) both for single and multi-fractionated irradiation. The mechanism(s) of **nitroxide**-mediated radioprotection is at present unknown.
RN 11062-77-4 (Superoxides); 20537-88-6 (Amifostine); **2226-96-2 (2,2,6,6-tetramethyl-4-piperidinol-N-oxyl)**; 7722-84-1 (Hydrogen Peroxide); 9007-49-2 (DNA)
CN 0 (Cyclic N-Oxides); 0 (Hematopoietic Cell Growth Factors); 0

(Radiation-Sensitizing Agents); 0 (Stem Cell Factor)

L169 ANSWER 7 OF 7 CANCERLIT
AN 81629501 CANCERLIT
DN 81629501
TI EFFECT OF GAMMA RADIATION ON THE TRANSPORT OF SPIN-LABELED COMPOUNDS ACROSS THE ERYTHROCYTE MEMBRANE.
AU Gwozdzinski K; Bartosz G; Leyko W
CS Dept. Biophysics, Inst. Biochemistry and Biophysics, Univ. Lodz, Banacha 12/16, PL-90-237 Lodz, Poland.
SO Radiat Environ Biophys, **(1981)**. Vol. 19, No. 4, pp. 275-285.
DT Journal; Article; (JOURNAL ARTICLE)
FS ICDB
LA English
EM 198112
AB Transport of spin-labeled compounds into bovine RBC was studied. The compounds used included 2,2,6,-tetramethylpiperidine-1-oxyl (**TEMPO**), 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (**TEMPOL**), **TEMPOL**-choline, and 3-carboxy-2,2,6,6-tetramethylpyrrolidine-1-oxyl. Irradiation of the RBC in the dose range of 2-50 kilorad resulted in a regular dose-dependent increase in the reduction rates of **TEMPO**-choline (a cation), and **TEMPO** (a hydrophobic non-electrolyte), and nonregular changes in the reduction rate of **TEMPOL** (a hydrophilic non-electrolyte). The permeation constant for **TEMPO**-choline showed a non-regular response to radiation similar to the response of other RBC parameters. The effects of the radiation on the transport of various solutes can be used as a means of distinguishing between different channels of membrane transport. (19 Refs)
CN 0 (Spin Labels)